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Thrombo-embolism in Acute and in Healed Myocardial Infarction

I. Intracardiac Mural Thrombosis*

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This is a study of the location and incidence of intracardiac thrombi in acute and in healed myocardial infarction. In myocardial infarction intracardiac thrombi occur predominantly in the left ventricle. Anterior myocardial infarcts are more commonly associated with mural thrombi than posterior myocardial infarcts. Large myocardial infarcts and congestive failure are factors which predispose to the formation of left ventricular mural thrombi in myocardial infarction.

IN RECENT YEARS considerable interest has centered on attempts at prevention of the thrombo-embolic complications of acute myocardial infarction. The incidence of thrombotic and embolic lesions in cases of acute myocardial infarction has been found to be high,[2-8] ranging from 6.5 per cent[9] to 60 per cent.[5]

Intracardiac mural thrombosis occurs frequently after myocardial infarction and is a factor in the production of systemic arterial occlusion.[2, 3, 6, 10-12] This study was undertaken to determine some of the factors involved in the formation of intracardiac mural thrombi in myocardial infarction. It is a clinical and pathologic analysis of data on 327 cases of acute or healed myocardial infarction. Anticoagulants had not been used in any of the cases in this study.

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* The second paper of this series[1] reports a study of systemic and pulmonary arterial occlusion in the same series of cases.

Material and Methods

There were 210 consecutive cases of acute fatal myocardial infarction in 110 of which there were healed myocardial infarcts as well. In addition 117 consecutive fatal cases in which healed myocardial infarcts were found were studied.

The term "acute myocardial infarct," as used in this study, indicates any infarct which by clinical and histologic evidence appeared to have occurred less than six weeks before death.

In each case with an acute myocardial infarct death was considered to be related to the existence of the infarct. The cases with healed myocardial infarction alone were obtained from a consecutive series of routine necropsy examinations. While some of these patients died of causes related to coronary arterial disease, many died of unrelated causes.

The data in each case were derived from study of the clinical history, of the necropsy protocol, of the gross specimen of the heart, which had been preserved in each case, and of histologic sections of the heart.

Results

In this study the majority of the intracardiac mural thrombi were found in the left ventricle. There were 108 cases, or 33 per cent of the series, in which left ventricular mural thrombi were present. Mural thrombi were found in

the right ventricle in nine instances. In 31 cases mural thrombi were found in one or both auricular appendages.

Most of the left ventricular mural thrombi were situated at or near the apex of the ventricle and often extended onto the anterior wall or the anterior portion of the ventricular septum. In all of the cases having anterior infarcts the left ventricular thrombi involved the apex or the anterior wall of the left ventricle or both. The majority of the left ventricular thrombi found in the cases of posterior infarction were located at the apex of the ventricle; however, in a few instances the mural thrombi were attached to the posterior wall of the ventricle over the infarct.

TABLE 1.—*Comparative Incidence of Left Ventricular Mural Thrombosis in Acute and in Healed Myocardial Infarction*

Age of Infarct	Cases	With Left Ventricular Mural Thrombi	
		Cases	Per cent
Acute infarct only	100	37	37.0
Acute infarct with healed infarct	110	43	39.1
Healed infarct only	117	28	23.9
Total	327	108	33.0

In nearly all of the hearts having left ventricular mural thrombi, histologic examination revealed evidence of infarction of the myocardium underlying the thrombi. This was true also of the posterior infarcts with thrombi situated at the apex of the ventricle. In these hearts the posterior infarct was found to involve the apex as well as the basal portions of the posterior wall of the ventricle.

Because of the great preponderance of left ventricular mural thrombi, particular attention was paid to the cases with thrombi in this chamber. An attempt was made to evaluate the influence of various factors on the formation of mural thrombi in the left ventricle. The factors investigated were the age of the infarct, its location in the ventricular wall, its size, and the effect of congestive heart failure, of cardiac hypertrophy and of auricular fibrillation.

Left ventricular mural thrombi were found more frequently in the cases of acute myocardial infarction than in those cases with healed infarcts. Of the 210 cases having acute myocardial infarcts, 80 were found to have left ventricular thrombi (38 per cent). Of 117 cases of healed infarction there were 28 cases with thrombi in the left ventricle (24 per cent) (table 1).

The location of the infarct in the left ventricle appeared to have a rather marked effect on the incidence of mural thrombi in that chamber of the heart. There were 115 cases with acute infarcts alone, or acute and healed infarcts coexisting, in the anterior left ventricular wall. Forty-eight of these (41.7 per cent) were found to have left ventricular thrombi. There were 52 cases either with acute infarcts alone, or acute and healed infarcts coexisting, in the posterior wall of the left ventricle. Of these there were 11 cases (21.2 per cent) with mural thrombi in the left ventricle. Among the cases of healed myocardial infarction alone there were 60 cases having anterior infarcts, of which 18 (30 per cent) were found to have left ventricular thrombi. There were 49 cases of healed posterior infarction, of which eight cases (16.3 per cent) were found to have mural thrombi in the left ventricle. There were 51 cases in which there were infarcts in both the anterior and posterior walls. These were not included in the study on the effect of location of the infarct on the incidence of left ventricular thrombi.

In order to determine the relationship of the size of the myocardial infarct to the frequency of left ventricular mural thrombosis, the length of each infarct was multiplied by its width and the product was assumed to be the approximate area involved by the infarct. Using this method it appeared that as the total area involved by the infarct increases, so does the incidence of mural thrombi in the left ventricle (table 2). There were 240 cases in which the area of myocardial infarction was less than 40 sq. cm.*

* The dividing point between large and small infarcts in this study was arbitrarily set at 40 sq. cm. Most of the cases were found to have infarcts of less than 80 sq. cm. in area; hence it seemed logical to select the half-way mark as the dividing line.

Of these 240 cases there were 52 (21.7 per cent) in which mural thrombi were found in the left ventricle. In 87 cases with myocardial infarcts of 40 sq. cm. or more, there were left ventricular mural thrombi in 56 cases (64.4 per cent).

In evaluating the effect of congestive cardiac failure on the incidence of left ventricular mural thrombi it is apparent that our interest in this regard is with the patient who in the course of his illness with either acute or healed infarction showed clinical evidence of congestive failure persisting for at least several days. Cases of sudden terminal heart failure or death with acute pulmonary edema in which there had been no antecedent evidence of passive congestion either clinically or at necropsy were excluded from the category here classified as congestive cardiac failure.

TABLE 2.—*Relationship of the Size of the Myocardial Infarct to the Incidence of Left Ventricular Mural Thrombosis*

Size of Infarct	Cases	With Left Ventricular Mural Thrombi	
		Cases	Per cent
sq. cm.			
Less than 20	108	16	14.8
20–39	132	36	27.3
40–59	58	34	58.6
60–79	15	9	60.0
80 or greater	14	13	92.9
Total	327	108	33.0

The presence of congestive cardiac failure appeared to be associated with higher incidence of left ventricular mural thrombosis than was the absence of congestive failure. In the cases with acute myocardial infarction, 43 per cent of those having left ventricular thrombi had had congestive failure and 27 per cent of the cases having no left ventricular thrombi had had congestive failure. In the cases having both healed and acute infarcts, congestive failure had been present in 53 per cent of the cases with thrombi in the left ventricle, whereas the incidence of congestive failure was only 30 per cent in the cases with no left ventricular thrombi. The cases of healed infarction with left ventricular thrombi were found to have had congestive failure in 68 per cent as contrasted with an incidence of congestive failure of only 28 per cent in the cases with no left ventricular thrombi (table 3).

Most investigations would indicate that when hypertension coexists with myocardial infarction the prognosis is less favorable than when no hypertension is present. Because of this belief an attempt was made to ascertain if any relationship exists between hypertension and mural thrombosis in the left ventricle. Since it was not possible to determine from the clinical data in each case whether or not hypertension had been present, the weight of the heart was used as an index. In this study the heart was considered to be hypertrophied if its weight was found to be 50 per cent greater than the normal standard weight as calculated by the method of Smith.[13] Admittedly such a method is not entirely accurate; however, in the absence of some other obvious cause of hypertrophy such as a valvular lesion, it seemed to be the best single method of determining whether hypertension had been present. In the cases with acute myocardial infarction there was no significant difference in the incidence of hypertrophy between the group with left ventricular thrombi and the group having none, the incidences of hypertrophy being 57 and 56 per cent respectively. In the cases having acute infarction associated with healed infarction,

TABLE 3.—*Effect of Congestive Cardiac Failure on the Incidence of Left Ventricular Mural Thrombosis in Myocardial Infarction*

Age of Infarct	Left Ventricular Mural Thrombi	Cases	With Congestive Failure	
			Cases	Per cent
Acute infarct only	Present	37	16	43.2
	Absent	63	17	27.0
Acute infarct with healed infarct	Present	43	23	53.5
	Absent	67	20	29.8
Healed infarct only	Present	28	19	67.9
	Absent	89	25	28.1
Total		327	120	36.7

myocardial hypertrophy was found in 70 per cent of the cases with left ventricular thrombi as compared to a 40 per cent incidence of cardiac hypertrophy in the cases with no thrombi in the left ventricle. Myocardial hypertrophy was found in 75 per cent of the cases of healed infarction having left ventricular thrombi, and in 48 per cent of the cases with no mural thrombi (table 4).

There were only 27 cases in this study in which auricular fibrillation was proved. Since this number is so small, no accurate conclusion can be made with respect to the relationship of this arrhythmia to the formation of left ventricular mural thrombi. Mural thrombi were found in the left ventricle in only six of the 27 cases with auricular fibrillation. This is an incidence of about 22 per cent, which is slightly less than the incidence of left ventricular thrombi in the entire series (33 per cent).

TABLE 4.—*Relationship of Myocardial Hypertrophy to the Incidence of Left Ventricular Mural Thrombosis in Myocardial Infarction*

Age of Infarct	Left Ventricular Mural Thrombi	Cases	With Cardiac Hypertrophy	
			Cases	Per cent
Acute infarct only	Present	37	21	56.8
	Absent	63	35	55.5
Acute infarct with healed infarct	Present	43	30	69.8
	Absent	67	27	40.3
Healed infarct only	Present	28	21	75.0
	Absent	89	43	48.3
Total		327	177	54.1

Mural thrombi were found in the right ventricle in only nine instances. Acute myocardial infarction was present in eight of the nine cases, and in these eight cases there were mural thrombi in the left ventricle as well as in the right ventricle. In each case an infarct was found in the left ventricular wall extending to the right ventricular myocardium, the mural thrombus being attached to this area. In six cases there was an anterior infarct in the left ventricle which extended into the ventricular septum and the adjacent right ventricular anterior wall. In each of the three remaining cases there was a left ventricular posterior infarct extending into the ventricular septum and the posterior wall of the right ventricle. Congestive cardiac failure had been present in 5 of the 9 cases with mural thrombi in the right ventricle.

In this study auricular mural thrombi were found rather infrequently. In the group of 210 cases with acute myocardial infarction there were 20 cases (9.5 per cent) with auricular mural thrombi. Of 117 cases with healed myocardial infarction there were 11 cases (9.4 per cent) with auricular mural thrombi. In all instances the auricular mural thrombi were restricted to the auricular appendages.

TABLE 5.—*Auricular Mural Thrombi in 210 Cases of Acute Myocardial Infarction*

Location of Mural Thrombi	Cases	Associated Thrombi of Left Ventricle	With Congestive Failure		With Auricular Fibrillation	
			Cases	Per cent	Cases	Per cent
Right atrium only	9	6	4	44.4	1	11.1
Left atrium only	7	4	3	42.9	0	0
Right and left atria	4	4	2	50.0	0	0
Total	20	14	9	45.0	1	5.0

TABLE 6.—*Auricular Mural Thrombi in 117 Cases of Healed Myocardial Infarction*

Location of Mural Thrombi	Cases	Associated Thrombi of Left Ventricle	With Congestive Failure		With Auricular Fibrillation	
			Cases	Per cent	Cases	Per cent
Right atrium only	8	6	8	100.0	3	37.5
Left atrium only	1	0	0	0	1	100.0
Right and left atria	2	0	2	100.0	0	0
Total	11	6	10	90.9	4	36.4

In the group with acute myocardial infarction mural thrombi were found with slightly greater frequency in the right auricular appendage than in the left auricular appendage. In the cases with healed myocardial infarction

most of the auricular thrombi were found in the right auricular appendage (tables 5 and 6).

Congestive cardiac failure had been present in nine of the 20 cases (45 per cent) of acute myocardial infarction with auricular mural thrombi. In 10 of the 11 cases (91 per cent) of healed infarction with auricular thrombi congestive failure had been present (tables 5 and 6).

Auricular fibrillation had been present in only one of the 20 cases of acute myocardial infarction having auricular mural thrombosis. In the 11 cases of healed infarction having auricular mural thrombi, auricular fibrillation had occurred in four instances (tables 5 and 6).

Comment

From this study it would appear that several factors are related to mural thrombosis in the left ventricle in myocardial infarction: (1) the age of the infarct, (2) the location of the infarct, (3) the size of the infarct, (4) the presence of congestive cardiac failure, (5) the presence of myocardial hypertrophy.

Doubtless these factors are interdependent in their influence on the formation of mural thrombi in the left ventricle. For example, it might be expected that the greater incidence of left ventricular thrombi in acute myocardial infarction, as compared with the incidence in healed infarction, could be due partially to the fact that the infarcts are more extensive in the former type of case than in the latter. The patient with a large acute myocardial infarct is more likely to die of the disease than the patient with a small infarct, and his case is thus designated as one of acute infarction. On the other hand, the patient with a small acute myocardial infarct may survive the infarction, and later when he dies and necropsy is performed the infarct is in the healed stage, and his case is thus categorized as one of healed infarction.

In 210 cases of acute myocardial infarction there were 64 instances (30.5 per cent) in which the infarcts were 40 sq. cm. or more in size, whereas in 117 cases of healed infarction there were 23 (19.6 per cent) cases in which the infarcts were 40 sq. cm. or more in area.

It might also be expected that the incidence of congestive cardiac failure would be greater in the cases having large myocardial infarcts than in those having small infarcts. Those cases with myocardial hypertrophy would also be expected to be associated with congestive failure more often than would those cases having normal cardiac weights. Both of these hypotheses were tested in 200 consecutive cases of myocardial infarction.* In 88 cases found to have no myocardial hypertrophy, congestive failure had been present in 15 cases (17 per cent), whereas in 112 cases with myocardial hypertrophy, congestive failure had occurred in 60 instances (53.6 per cent). Of the same 200 cases, in 140 having myocardial infarcts less than 40 sq. cm. in area, there were 45 in which there had been congestive failure (32.1 per cent). There were 60 cases having infarcts of 40 sq. cm. or larger, in 30 of which (50 per cent) there had been congestive failure.

There may be several reasons for the greater incidence of left ventricular mural thrombi in the cases with anterior myocardial infarction as compared to those with posterior infarction. Infarcts of the anterior wall of the left ventricle very often involve the apex of the ventricle as well. When there is incomplete ejection of blood from the ventricle, such as might occur in the presence of a large myocardial infarct or in congestive heart failure, the apex of the ventricle may then be a site of stasis of blood and thus might predispose to the formation of mural thrombi. The majority of posterior myocardial infarcts tend to occur near the base of the left ventricle, well away from the apex. An additional factor may be that the posterior infarcts in this study were in general found to be smaller than the anterior infarcts. In 200 consecutive cases of myocardial infarction* there were 77 hearts having only posterior infarcts, of which 13 (17 per cent) were found to be 40 sq. cm. or larger in area. There were 103 hearts having only anterior infarcts, of which 38 (37 per cent) were 40 sq. cm. or larger in size.

Probably the two most important factors

* This included 117 cases of healed myocardial infarcts, 48 cases with acute infarcts alone and 35 cases in which acute and healed myocardial infarcts coexisted.

influencing the formation of left ventricular mural thrombi in cases of myocardial infarction are the presence of congestive cardiac failure and the presence of a large myocardial infarct. Each of these factors tends to prevent complete emptying of blood from the ventricular chamber.

Summary and Conclusions

1. Data on 327 cases of myocardial infarction in which necropsy was performed have been analyzed with respect to the incidence of intracardiac mural thrombi and to the various factors influencing the formation of intracardiac mural thrombi.

2. The incidence of left ventricular mural thrombi was greater: (a) in acute infarction as compared with healed infarction; (b) in anterior infarction as compared with posterior infarction; (c) when congestive cardiac failure was present than when it was absent; (d) when cardiac hypertrophy was present than when it was absent; (e) in cases having large infarcts as compared with cases having small infarcts.

3. The factors listed appear to be interrelated, and it is believed that the greatest single factors are those producing stasis of blood in the heart; that is, congestive failure and the size of the myocardial infarct have the greatest influence in formation of left ventricular mural thrombi.

4. Mural thrombi were found infrequently in the right ventricle. When thrombi were found in this location, they were usually associated with left ventricular mural thrombi.

5. Auricular mural thrombi were found in a small number of cases and usually were associated with congestive cardiac failure.

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Thrombo-embolism in Acute and in Healed Myocardial Infarction

II. Systemic and Pulmonary Arterial Occlusion

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The purpose of this investigation was to study the incidence and location of systemic arterial occlusion and pulmonary embolism in a consecutive series of cases of fatal acute myocardial infarction. Another consecutive series of cases in which healed myocardial infarction was demonstrated at necropsy was similarly studied. In none of the cases included in this study had anticoagulant therapy been employed.

Massive pulmonary embolism was the most frequent fatal thrombo-embolic complication found among the cases of acute myocardial infarction. Cerebral infarction was the most frequent fatal thrombo-embolic complication found among the cases of healed myocardial infarction. Cerebral infarction was the most frequent fatal systemic arterial thrombo-embolic lesion in both groups. Acute splenic and renal infarcts were frequently demonstrated but with one exception appeared to play an incidental role in the clinical course of the patients. Although systemic arterial occlusion was frequently found in association with intracardiac mural thrombi, there were many other cases in which evidence of systemic arterial occlusion was found in the absence of intracardiac mural thrombi. A positive correlation existed between the presence of pulmonary and systemic arterial occlusion and the occurrence of congestive cardiac failure.

THROMBOSIS and embolism in the systemic and pulmonary arteries are grave complications associated with myocardial infarction. Symptoms of these complications usually appear suddenly but may be insidious in onset. They may occur during the acute phase of myocardial infarction when the patient is acutely ill from his cardiac lesion or several weeks to months later when the patient has apparently recovered from acute myocardial infarction. Occasionally signs of arterial embolism may be the outstanding feature in a case of acute myocardial infarction.[1] Systemic and pulmonary arterial occlusions in cases of myocardial infarction have come to be of particular interest in recent years with the advent of the use of heparin, dicumarol and other anticoagulant agents in efforts to prevent these complications.[2-6]

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The present study was undertaken to determine the incidence of pulmonary embolism and of systemic arterial insufficiency in myocardial infarction as observed at necropsy in cases in which anticoagulants had not been used. Furthermore, since some clinicians feel that anticoagulants should not or cannot, because of limited facilities, be used routinely in all cases of acute myocardial infarction, a definite effort was made to observe the conditions under which thrombo-embolic complications are more likely to occur. It was also desired to ascertain the relationship of systemic arterial insufficiency to the presence or absence of thrombi in the left side of the heart. The cases employed, totaling 327, are identical with those reported by us[7] regarding the incidence and location of intracardiac thrombi in myocardial infarction.

Material and Methods

The material consisted of 327 cases of acute or of healed myocardial infarction in which necropsy was performed. Two hundred and ten of these cases were classified as acute myocardial infarction. In each of these cases there was an acute myocardial

infarct and in 110 of these there were healed myocardial infarcts as well. In 117 cases, only healed myocardial infarcts existed.

In each case with an acute myocardial infarct death was considered to be related to the existence of the infarct. The cases with healed myocardial infarction alone were obtained from a consecutive series of routine necropsy examinations. While some of these patients died of causes related to coronary arterial disease many died of unrelated causes. None of the patients had received anticoagulants.

In each case included in this study the heart was available for re-examination as to the age and location of the infarct and the occurrence of intramural thrombosis. Clinical and necropsy records, histologic sections and in some instances gross specimens of additional organs were also available for the study of the incidence and nature of extracardiac thrombo-embolic complications. The age of the infarct in each case was based on the clinical history and on the histologic criteria of Mallory and associates.[8] Those cases in which the infarct appeared to be less than six weeks old were classified as acute myocardial infarction. The remainder of the cases were classified as healed myocardial infarction. In almost all the cases in the latter group the infarcts appeared to be several months to years old. The diagnosis of arterial occlusion was based entirely on pathologic observations. This diagnosis was made on the demonstration of a thrombus or embolus in an artery or typical changes of recent infarction of a particular organ. In many cases it was impossible to determine whether a mass of thrombotic material occluding an artery was a thrombus formed in situ or an embolus. In still other circumstances no thrombotic material could be found in arteries leading to a zone of obvious recent infarction. Whenever either thrombotic material was found in an artery or an area of recent infarction was demonstrated in an organ even without demonstration of an occluded artery, the case was classified as one of acute arterial occlusion. In each case ventricular mural thrombosis and congestive failure were noted in order to determine their significance in the occurrence of these "thrombo-embolic" complications.

Incidence of Systemic and Pulmonary Arterial Occlusion in Myocardial Infarction (Table 1)

Of the 327 cases studied in this series 58 patients (18 per cent) at necropsy were found to have one or more pulmonary arterial occlusions with or without pulmonary infarction.

There were 210 cases in which the myocardial infarction was classified as acute. Of these, there were 33 (16 per cent) who were found to have pulmonary embolism. A slightly higher incidence of pulmonary arterial occlusion was found among cases of healed infarction. Of the 117 cases of healed myocardial infarction 25 patients (21 per cent) were found to have pulmonary embolism of varying degrees of severity.

Evidence of systemic arterial occlusion in one or more locations was found in 84 patients (26 per cent) of the total (327) cases studied.

The incidence of systemic arterial occlusion in acute myocardial infarction was 25 per cent (52 cases among a total of 210 patients). Among the patients with healed infarction, there was an incidence of systemic arterial occlusion of 27 per cent (32 cases among a total of 117 patients).

Table 1.—*Incidence of Pulmonary and Systemic Arterial Occlusion among 327 Cases of Acute or Healed Myocardial Infarction*

	Cases	Pulmonary Arterial Occlusion		Systemic Arterial Occlusion	
		No.	%	No.	%
Acute	210	33	16	52	25
Healed	117	25	21	32	27
Total	327	58	18	84	26

Table 2.—*Relation of Systemic and Pulmonary Arterial Occlusion to the Presence of Left-sided Intracardiac Mural Thrombi in 327 Patients with Acute or Healed Myocardial Infarction*

	Cases	Cases with Systemic Arterial Occlusion	
		No.	%
With mural thrombi	114	39	34
No mural thrombi	213	45	21
Total	327	84	26

Incidence of Systemic Arterial Occlusion in Patients with and without Intracardiac Mural Thrombi (Table 2)

Of the 327 cases, there were 114 having intracardiac mural thrombi. Of the 114 cases, 39 were found to have evidence of systemic arterial occlusion, an incidence of 34 per cent. Of the 213 cases in which the heart contained

no mural thrombi, there was an incidence of systemic arterial occlusion of 21 per cent (45 among 213 cases).

Incidence of Systemic and Pulmonary Arterial Occlusion in Acute Myocardial Infarction

Eighty-three of the 210 hearts from patients with acute myocardial infarction contained left-sided cardiac mural thrombi, 80 of which were

Table 3.—*Incidence of Systemic Arterial Occlusion in Patients with Fatal Acute Myocardial Infarction: Relation of Mural Thrombosis to Systemic Arterial Occlusion*

	Cases	With Systemic Arterial Occlusion		Without Systemic Arterial Occlusion	
		Cases	%	Cases	%
Left-sided cardiac mural thrombi present	83	29	35	54	65
Left-sided cardiac mural thrombi absent	127	20	16	107	84
Total	210	49	23	161	77

Table 4.—*Relation of Congestive Failure to Incidence of Systemic Arterial Occlusion in 210 Cases of Fatal Acute Myocardial Infarction*

	Cases	With Congestive Failure		Without Congestive Failure	
		Cases	%	Cases	%
Systemic arterial occlusion present	49	28	57	21	43
Systemic arterial occlusion absent	161	48	30	113	70
Total	210	76	36	134	64

left ventricular alone or associated with a thrombus in the left atrium, and three in which only left auricular mural thrombi were found. In 29 (35 per cent) of the 83 cases of left-sided cardiac mural thrombi a pathologic diagnosis of systemic arterial occlusion was made. However, of the remaining 127 patients with acute myocardial infarction but without left-sided mural thrombi 20 (16 per cent) fulfilled the criteria for a diagnosis of systemic arterial occlusion (table 3). Congestive failure was nearly twice as frequent in the patients with systemic arterial occlusion (57 per cent) as compared with the patients without systemic arterial occlusion (30 per cent) (table 4). This greater incidence of congestive failure in patients with systemic arterial occlusion as compared with those without systemic arterial occlusion was similar both in the group with and the group without left-sided cardiac mural thrombi. Sev-

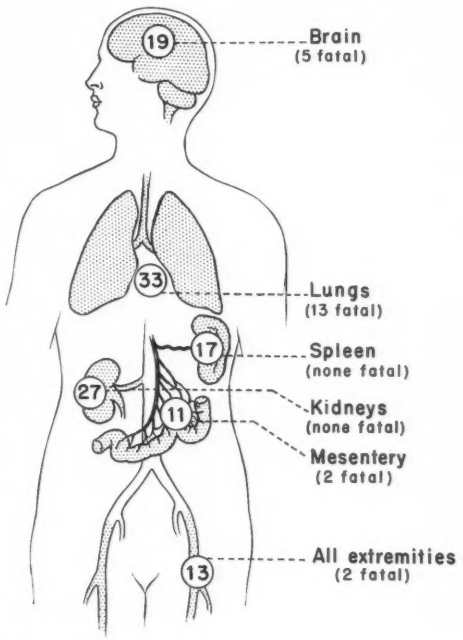

Fig. 1. Incidence and location of systemic and pulmonary arterial "occlusions" in the 52 patients having vascular "occlusions" among 210 cases of acute myocardial infarction.

enty-six patients with acute myocardial infarction showed evidence of congestive failure. In this group systemic arterial occlusions were found in 37 per cent of the cases. By comparison 134 patients with acute myocardial infarction showed no evidence of congestive failure. In these patients the incidence of systemic arterial occlusion was only 16 per cent. There were 87 organs or extremities with systemic arterial occlusion found in 52 patients (fig. 1). Thus, multiple lesions of this nature occurring in one patient were common. In 23 of the 87 organs involved in systemic arterial occlusion there

was clinical evidence of this complication. In nine patients systemic arterial occlusion was considered to be a major factor causing death (4 per cent of 210 cases). Of these nine cases there were two in which major arteries to the lower extremities were occluded, two in which superior mesenteric arterial occlusion had occurred and five in which a major cerebral artery was occluded. In one of the latter five cases an embolus was demonstrated at the site of arterial occlusion. The other four occlusions were thrombotic in nature and related to rather severe cerebral atherosclerosis.

Pulmonary embolism or infarction was present in 33 cases (16 per cent of 210 cases of acute myocardial infarction) (fig. 1). In six of these 33 cases sudden death was caused by massive pulmonary embolism. In seven other cases pulmonary embolism (with or without infarction) was relatively large, causing occlusion of an artery supplying the major portion of one lobe, and was considered a major factor contributory to death. The remainder of the pulmonary thrombo-embolic lesions consisted of small pulmonary infarcts which apparently played only a minor role, if any, as a cause of death. Pulmonary embolism and infarction were found in five of the eight cases of acute myocardial infarction with mural thrombi in the right ventricle. In none of these cases did pulmonary embolism appear to have caused sudden death. In one of the five cases there were numerous small pulmonary emboli and infarcts which were considered to have been contributory to death. In three additional cases with right ventricular mural thrombi pulmonary embolism was not present.

TABLE 5.—*Incidence of Pulmonary Embolism in 210 Fatal Cases of Acute Myocardial Infarction*

	Cases	With Congestive Failure		Without Congestive Failure	
		Cases	%	Cases	%
Pulmonary embolism present	33	22	67	11	33
Pulmonary embolism absent	177	54	31	123	69
Total	210	76	36	134	64

Of the 33 patients with pulmonary embolism or infarction 22 (67 per cent) had had congestive failure (table 5). Of the 177 patients without pulmonary thrombo-embolism only 54 (31 per cent) had had congestive failure. Seventy-six of the 210 cases of acute myocardial infarction showed evidence of congestive failure. Of these 76 cases with congestive failure complicating acute myocardial infarction 22 (29 per cent) were complicated by pulmonary embolism or infarction.

INCIDENCE OF SYSTEMIC AND PULMONARY ARTERIAL OCCLUSION IN HEALED MYOCARDIAL INFARCTION

This portion of the study dealt with 117 consecutive cases in which necropsy demonstrated healed myocardial infarction. There was no significant difference between the incidence of systemic arterial occlusion among those cases with and those without left-sided cardiac mural thrombosis (table 6). Among 31 cases with left-sided cardiac mural thrombi eight cases showed systemic arterial occlusion (26 per cent). Of 86 cases without left-sided cardiac mural thrombi systemic arterial occlusion was observed in 24 cases (28 per cent). There were 45 organs involved by systemic arterial occlusion in 32 patients with healed myocardial infarction. In 11 of the patients these complications were considered to be of major significance in causing death (fig. 2). In 29 patients the complication was clinically evident, being cerebral in 20 instances, extremital in seven and mesenteric in two (fig. 2). It is of interest that

TABLE 6.—*Incidence of Systemic Arterial Occlusion in 117 Fatal Cases in which Healed Myocardial Infarcts Were Found*

	Cases	With Systemic Arterial Occlusion		Without Systemic Arterial Occlusion	
		Cases	%	Cases	%
Left-sided cardiac mural thrombi present	31	8	26	23	74
Left-sided cardiac mural thrombi absent	86	24	28	62	72
Total	117	32	27	85	73

among the 20 patients with cerebral infarcts, occlusion of a cerebral artery by thrombotic material was found in only four. In the remaining 16 cases only severe localized atherosclerosis was found. There was no significant difference in the incidence of congestive failure between those cases with and those cases without systemic arterial occlusion (table 7). Of 32 patients with systemic arterial occlusion 14 (44 per cent) had congestive failure while among 85 patients without systemic arterial occlusion 30 (35 per cent) had congestive failure. However, 22 patients without congestive failure had had a recent major operation or severe trauma while only two patients with congestive failure had had a recent operation. These complicating circumstances appeared to nullify the effect of congestive failure on the presence of systemic arterial occlusion in the group of cases with healed myocardial infarcts as compared with the positive correlation in patients with acute myocardial infarction.

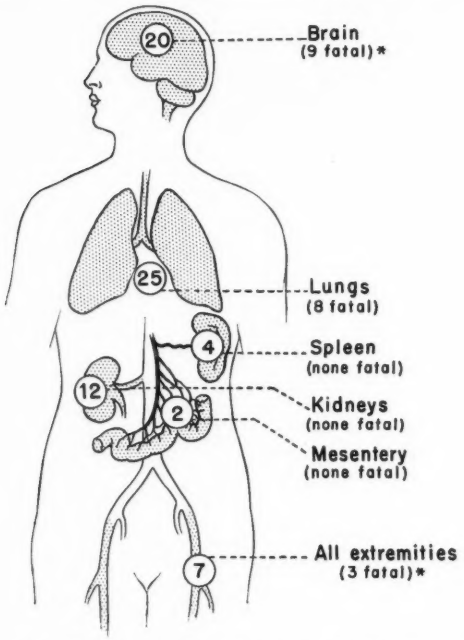

FIG. 2. Incidence and location of systemic and pulmonary arterial "occlusions" in the 32 patients having vascular occlusions among 117 cases of healed myocardial infarction.

* Total fatal cases of systemic arterial occlusion numbered 11. In one case occlusion of a femoral artery with gangrene of the leg and a cerebral infarct coexisted.

Pulmonary embolism or infarction was found in 25 of the 117 cases with healed myocardial infarction (21 per cent). In 11 of these cases the emboli were clinically evident, eight being massive and causing sudden death. In eight of these 11 cases there was a history of recent major operation for cancer or fracture of an extremity. The remaining three cases manifested congestive failure alone, which was probably related in part to the healed myocardial infarct. Right ventricular mural thrombi were not found in any of the cases with healed myocardial infarction and pulmonary embolism or infarction. Evidence of thrombosis in the veins of the lower extremities or pelvis was found in most of the cases with fatal pulmonary embolism.

TABLE 7.—*Relation of Congestive Failure to Incidence of Systemic Arterial Occlusion in 117 Fatal Cases in which Healed Myocardial Infarcts Were Found*

	Cases	With Congestive Failure		Without Congestive Failure	
		Cases	%	Cases	%
Systemic arterial occlusion present	32	14	44	18	56
Systemic arterial occlusion absent	85	30	35	55	65
Total	117	44	38	73	62

COMMENT

The ultimate purpose of this study was to demonstrate anatomically the incidence and location of pulmonary and systemic arterial occlusion in a consecutive series of cases of fatal acute myocardial infarction. Another consecutive series of cases in which healed myocardial infarction was demonstrated at necropsy was similarly studied to determine the nature of these vascular complications. It should be re-emphasized that in none of these cases were anticoagulants used as part of the therapy. It is hoped that this will serve in part as a control study for a review of a group of cases of fatal

myocardial infarction in which anticoagulants were used.

This study did not include venous thromboses of the extremities without pulmonary embolism, for many of these extremital venous lesions were out of reach of routine necropsy dissection. When pulmonary embolism or infarction occurred in the absence of mural thrombosis in the right side of the heart, systemic venous thrombosis was considered the most likely source of this complication, and in many instances venous thromboses could be demonstrated. However, since venous thrombosis could not always be demonstrated anatomically, a statistical study of this complication, *per se*, was not undertaken.

Bean[9] has reported pulmonary arterial occlusion in 75 per cent of cases of myocardial infarction in which there was right ventricular mural thrombosis, and he compared this with an incidence of systemic arterial occlusion occurring in only 34 per cent of cases with left ventricular mural thrombosis. Similarly, we found pulmonary infarcts in five of eight cases of acute myocardial infarction with right ventricular mural thrombi. Yet, in none of these five cases was there massive pulmonary embolism. We feel that the chief danger of major embolization of the pulmonary arteries in acute myocardial infarction lies in venous thrombosis, particularly of the lower extremities. In all our cases of massive pulmonary embolism the thrombotic material was of such configuration that it appeared to have been formed in a large systemic vein and was coiled on itself in the major pulmonary arteries. In none of the cases with right ventricular mural thrombi was the pulmonary embolism of this nature. Usually a portion of one lobe was infarcted and the lesion did not appear to have played a dominant role in the clinical course.

In the interest of proper perspective concerning the nature of the systemic arterial occlusion it should be emphasized that interruption of adequate blood flow may be produced by embolism, thrombosis in situ or atherosclerotic narrowing alone or associated with shock or local alterations in blood flow. The latter possibility is particularly likely in cases of infarction of the brain affecting elderly patients with cerebral atherosclerosis. This type of peripheral arterial insufficiency may occur with acute myocardial infarction or with healed myocardial infarction complicating postoperative recovery or an acute infectious process.

In support of the postulate that many arterial occlusions are due to thrombus in situ or atherosclerotic narrowing is the fact that while acute infarction in areas supplied by systemic arteries occurred in 26 per cent of patients with healed myocardial infarction and intracardiac mural thrombi, this complication occurred in 28 per cent of patients with healed myocardial infarction but without intracardiac mural thrombi. While it may be assumed that some of these systemic arterial occlusions, in the absence of mural thrombi in the left side of the heart, represent embolization by the dislodgement of an entire intracardiac mural thrombus, it is unlikely that all of these lesions are examples of this phenomenon.

Evidence that many systemic arterial occlusions are embolic in origin may be had by using these same figures and comparing them with the incidence of systemic arterial occlusion in acute myocardial infarction. Among patients with acute myocardial infarction, arterial occlusion was more than twice as common when intracardiac mural thrombi were present (35 per cent) as when mural thrombi were absent (16 per cent). Among patients with healed myocardial infarcts, there was no significant difference between the incidence of systemic arterial occlusion in those cases with and those without intracardiac mural thrombi. Blumer[10] has stressed the difficulty encountered in determining anatomically at necropsy whether a given lesion is thrombotic or embolic in origin.

In reporting the incidence of thrombo-embolic complications of acute or healed myocardial infarction it is of equal importance to ascertain the significance of the various lesions as possible causes of death.[11] Forty-four of the 87 systemic arterial occlusions associated with acute myocardial infarction involved the spleen or kidneys. Only one of these 44 lesions was clinically evident. In this case embolization to a branch of the left renal artery produced infarction of the inferior half of the left kidney, causing severe, steady pain in the flank. This

complication seemed a contributory cause of death. Recent splenic and renal infarcts are frequently found incidentally at necropsy, particularly in association with congestive failure without acute myocardial infarction. Many of the splenic and renal infarcts found in this series were probably of coincidental etiologic relationship to the myocardial infarction and, more than likely, had little effect on the clinical course in the cases in which they occurred.

In many reports of clinical studies a frequent thrombo-embolic complication listed is that of a "second coronary thrombosis," "extension of the myocardial infarct" or like designations.[2-5, 12] It will be noticed that in this report this designation is not made, for the reasons indicated in the following paragraphs.

It is not uncommon during convalescence from acute myocardial infarction for patients to manifest attacks of precordial pain, sweating and tachycardia. Such attacks may even be associated with additional electrocardiographic changes. That such attacks indicate a poor prognosis is accepted.[13, 14]

Nevertheless, a diagnosis of a second coronary thrombosis on such findings is not justifiable in every case. The initial myocardial infarct itself might have occurred in the absence of intravascular thrombosis but as a result of ischemia secondary merely to coronary atherosclerosis. This phenomenon, the occurrence of acute myocardial infarction in the absence of coronary thrombosis, has been demonstrated in one sixth[15] to one third[16, 17] of the cases among several series of patients with acute myocardial infarction. Furthermore, recurrent thoracic pain may be due to repeated episodes of coronary insufficiency with or without infarction and not to so-called thrombo-embolic complications. In examining a large number of hearts of patients who had died of acute myocardial infarction we have found relatively few cases in which two acute infarcts of distinctly different ages could be demonstrated histologically even in those cases with histories of recent recurrent precordial pain.

In regard to propagation of a coronary thrombus as a cause of further acute myocardial infarction we have found very few thrombi more than 1 cm. in length and then only occasionally in the right coronary artery. The short course of a thrombus along a coronary artery has been pointed out by others and technics of dissection of these arteries have been proposed in order to avoid overlooking thrombi at necropsy. It seems unlikely that coronary arterial thrombi tend to propagate. Thus it would seem that the main danger of intravascular thrombosis during convalescence following acute myocardial infarction lies in the walls of the cardiac chambers and in the systemic arteries and veins, but not in the coronary arteries.

In our cases of fatal acute myocardial infarction systemic and pulmonary arterial occlusion occurred as a major or lethal complication in 10 per cent of the 210 cases. Systemic arterial occlusion was considered to have been a major cause of death in nine cases of the group of 210 patients with acute myocardial infarcts (4 per cent). Pulmonary embolism caused sudden death in 3 per cent of 210 cases with acute myocardial infarcts and played a major role in the death of an additional 3 per cent of the patients. Thus, pulmonary embolism comprised the largest portion of these major vascular complications. Similarly, this relatively high incidence of pulmonary embolism among the occlusive vascular complications of acute myocardial infarction has been noted by Conner and Holt,[18] Rosenbaum and Levine,[13] Woods and Barnes,[19] Nay and Barnes,[12] Mintz and Katz[14], Harrington and Wright,[20] Doscher and Poindexter[11] and Hellerstein and Martin.[21]

The distribution of systemic arterial occlusion was somewhat different in the group of cases with healed, as compared with the group with acute, myocardial infarcts. Cerebrovascular occlusion comprised a relatively larger portion of systemic arterial occlusions in the group with healed, as compared with the group having acute, myocardial infarcts. Furthermore, in all but three of the deaths in the group with healed myocardial infarcts which were due to systemic arterial occlusion a cerebral lesion was found exclusively. In two of the remainder, occlusion of an artery to a lower extremity was considered to be the fatal complication. In the eleventh case occlusion of a femoral artery with gangrene of the leg and a cerebral infarct coexisted.

Pulmonary embolism or infarction in the patients with healed myocardial infarction was usually related to some noncardiac factor such as a recent major operation, or severe trauma necessitating immobilization of the patient. However, in some of the cases with healed myocardial infarction congestive failure alone appeared to play a role in pulmonary thromboembolism.

Summary and Conclusions

1. A study was made of the incidence of systemic and pulmonary arterial occlusion in 210 cases of acute myocardial infarction and 117 cases of healed myocardial infarction.

2. Occlusion of a systemic artery or infarction of an organ may occur either in the presence or in the absence of left-sided intracardiac mural thrombi.

3. In acute myocardial infarction systemic arterial occlusion is more common when left-sided cardiac mural thrombi are present than when they are absent.

4. In acute myocardial infarction congestive cardiac failure favors the occurrence of systemic arterial occlusion.

5. In acute myocardial infarction congestive failure favors the occurrence of pulmonary embolism.

6. In healed myocardial infarction the incidence of systemic arterial occlusion was similar in the group with and the group without left-sided intracardiac mural thrombi, and there was found to be no greater incidence of systemic arterial occlusion in those cases having congestive failure than in those cases without congestive failure. The frequent occurrence of recent trauma or major operations in the group with healed myocardial infarction made the evaluation of congestive failure and its relation to the incidence of systemic arterial occlusion difficult.

7. Pulmonary embolism in some cases of healed myocardial infarction appeared to have been related to congestive cardiac failure. In many cases of healed myocardial infarction with and without congestive failure extracardiac factors such as recent trauma or major operations were related to the development of pulmonary embolism.

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The Effect of Arterialization of the Coronary Sinus in Dogs on Mortality Following Acute Coronary Occlusion

By R. W. Eckstein, M. D., George Smith, F. R. C. S., Morton Eleff, and James Demming

The mortality rates were determined in two groups of dogs following acute circumflex artery occlusion. Both groups were surgically prepared in the same manner. In a group of 20 dogs the coronary sinus was cannulated to divert the blood into the left jugular vein. Circumflex artery ligation resulted in 70 per cent mortality within one hour. In a second group of 10 dogs the coronary sinus was arterialized from the left subclavian artery and the sinus mean pressure was held at 50 mm. Hg. In this group circumflex artery ligation resulted in 100 per cent survival for one hour. Statistical analysis shows the results to be highly significant. The results strongly suggest that arterialization of the coronary sinus protects the hearts of dogs from ventricular fibrillation following coronary artery ligation.

AFTER some years of animal research Beck and his associates[1–4] have reported remarkable success in attempts to revascularize the heart. The technic at present employs a vein graft between the aorta and the coronary sinus. Some three weeks later the coronary sinus is partially occluded near its ostium. Following these procedures they have ligated a major branch of the coronary arterial system with a remarkably low mortality when compared with the mortality from coronary ligation in normal dogs. There is no doubt that these operations protect dogs from the generally disastrous effects of a major coronary occlusion. However, the mechanism of this protection has not been critically studied and at present is only theoretic.

Although elucidation of the details of this abnormal physiologic situation is desirable in chronic dogs, we have chosen to study the effects of acute arterialization of the coronary sinus in dogs on the acute mortality rate following acute coronary ligation. This study serves to answer the questions, (1) whether there is immediate protection resulting from arterialization of the coronary sinus or whether protection occurs only after some weeks and (2) whether the protection is due to extra coronary collaterals which grow into the myocardium during the development of scar tissue in the chronic dogs. Therefore, this report deals with a comparison of acute mortality statistics following acute circumflex artery occlusion between two groups of dogs, namely, those with acute arterialization of the coronary sinus and those without.

Methods

The following method was adopted after a group of experiments were done to develop a rapid and standard technic. Mongrel dogs whose weights varied between 8.2 and 26.1 Kg. were anesthetized with morphine and pentobarbital. Under artificial respiration the left chest was opened with a cautery between the fourth and fifth ribs. The pericardium was slit and the circumflex branch of the left coronary artery was isolated at its origin. A loose ligature was placed. The left subclavian artery was treated likewise. A ligature was passed about the coronary sinus near its ostium. The animal was heparinized*. The left jugular vein was cannulated and connected to the outflow side of the double lumen coronary sinus cannula (fig. 1). This cannula was then passed through the tip of the right auricle and tied securely into the coronary sinus. The left subclavian artery was cannulated and connected to the second lumen of the coronary sinus cannula. This connection was clamped until the preparation

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* The heparin was kindly supplied by Ben Venue Laboratories, Inc., Bedford, Ohio.

was complete. The aortic blood pressure was optically recorded through a cannula passed into the aorta through the left common carotid artery. Coronary sinus pressure was optically recorded from the exit lumen of the coronary sinus cannula. By means of a mercury manometer it was possible at all times to see the mean coronary sinus pressure. Electrocardiograms were taken and usually aV_R was used. The entire preparation was completed in from 30 to 45 minutes. An arterial and coronary sinus blood sample was drawn from most animals and analyzed for oxygen content by the method of Van Slyke and Neill.[5]

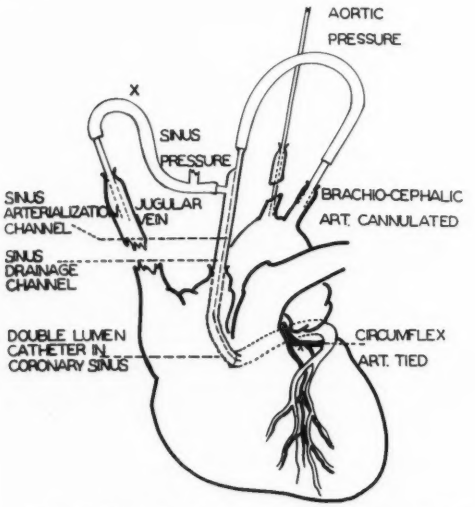

FIG. 1. Diagram showing double lumen cannula tied in ostium of coronary sinus with inflow connection to left subclavian artery and outflow connection to left jugular vein. Point X indicates application of clamp to maintain coronary sinus pressure of 50 mm. Hg.

Two groups of experiments were done. (A) This consisted of 10 dogs ranging in weight from 8.2 to 15.3 Kg. (average 10.1). In this group the connection between the left subclavian artery and the coronary sinus remained clamped, and the coronary sinus blood flowed into the left jugular vein without interposed resistance. After control aortic and sinus pressures and electrocardiograms were taken, the ligature about the circumflex artery was tied. Further pressures and electrocardiograms were taken and the fate of the animal was awaited. Those animals living more than 60 minutes were classed as survivals.

(B) There were 20 dogs in this group and these can be divided into two groups of 10 each, which were done alternately. (1) The dogs in this group ranged in weight from 9.5 to 26.1 Kg. (average 15.3) and were done exactly as in (A) above. (2) The second group consisted of dogs whose weights ranged from 9.1 to 25 Kg. (average 13.3) and were prepared as above. However, after control data were obtained the clamp between the left subclavian artery and the coronary sinus was removed and a screw clamp was tightened upon the outflow connection of the coronary sinus so as to maintain a mean coronary sinus pressure of 50 mm. Hg. After the blood pressure and electrocardiograms revealed no further change, the circumflex artery was ligated as before. A coronary sinus pressure of 50 mm. Hg was maintained and the death of the animal was awaited. At the close of the experiment the ligature was removed from the circumflex artery and a dilute solution of India ink was injected into it. The dyed area was cut out and weighed so as to relate the weight of the ischemic area to the total heart weight.

RESULTS

Group A

The results are shown in table 1. In this control group seven dogs died of ventricular fibrillation in an average time of 8.9 minutes. The remaining three dogs lived over 60 minutes and are classed as survivals. One of these died in 67 minutes with ventricular fibrillation and the remaining two were sacrificed after two hours. All dogs showed abnormal electrocardiograms after ligation of the circumflex artery.

Group B-1

In this group of alternate dogs without arterialization there were likewise seven deaths and three survivals. The deaths were all due to ventricular fibrillation in an average time of 7.9 minutes. The three surviving dogs were sacrificed: one in 70 minutes, one after 85 minutes, and one after three hours. All dogs showed abnormal electrocardiograms after circumflex artery ligation.

Group B-2

This entire group of 10 alternate dogs with arterialization of the coronary sinus under a pressure of 50 mm. Hg survived for 60 minutes. One of these died in 62 minutes in asystole and one died of ventricular fibrillation in three hours. In the remaining eight dogs, coronary sinus arterialization was discontinued at the end of 60 minutes with the return of sinus pressure to normal. Five of these dogs were

sacrificed in from one and one-half to two and one-half hours. However, the remaining three dogs developed ventricular fibrillation in 8, 10, and 17 minutes following discontinuation of coronary sinus arterialization. The typical electrocardiographic changes following arterialization of the sinus are shown in figure 2 *B*. These changes are usually minor and consist of a reduction in the amplitude of QRS complex with a flattening to a slight inversion of the T wave in aV_R. Displacement of the S-T segment has not been observed. Figure 2 *C* shows the typical changes following circumflex artery ligation in the presence of previous sinus arterialization.

TABLE 1.—*Showing Range and Averages of Dog Weight, Arterial Oxygen Content, Coronary Sinus A-V Oxygen Difference, Aortic Blood Pressure and Percentage of Total Heart Rendered Ischemic by Circumflex Ligation*

	Group A Control 10 Dogs		Group B-1 Control 10 Dogs		Group B-2 10 Dogs Arterialization of Coronary Sinus	
	Range	Average	Range	Average	Range	Average
Dog Weights (Kg.)	8.2– 15.3	10.1	9.5– 26.1	15.3	9.1– 25.0	13.3
Arterial Oxygen Content (Vol.%)	11.5– 19.3	15.7	8.4– 18.7	14.5	9.1– 17.7	13.7
Coronary Sinus A-V Difference (Vol.%)	9.8– 14.8	12.4	7.7– 12.9	11.2	7.1– 13.5	10.0
Percent of Total Heart Weight made Ischemic by Circumflex Ligation	36.0– 77.0	46.0	28.0– 38.0	35.0	33.0– 56.0	44.0
Mean Aortic Pressure (mm. of Hg) before Arterialization and Artery Ligation	47.0–137.0	87.8	48.0–138.0	99.4	74.0–140.0	95.1
Mean Aortic Pressure After Arterilization of Sinus					64.0–118.0	82.5
Time of Survival After Artery Ligation (minutes)	4.0– 60.0	24.2	2.0– 60.0	23.5		60.0
Time Until Ventricular Fibrillation Occurred (minutes)	3.0– 18.0	8.9	2.0– 37.0	7.9		
Percent Survival for 60 Minutes	30		30		100	

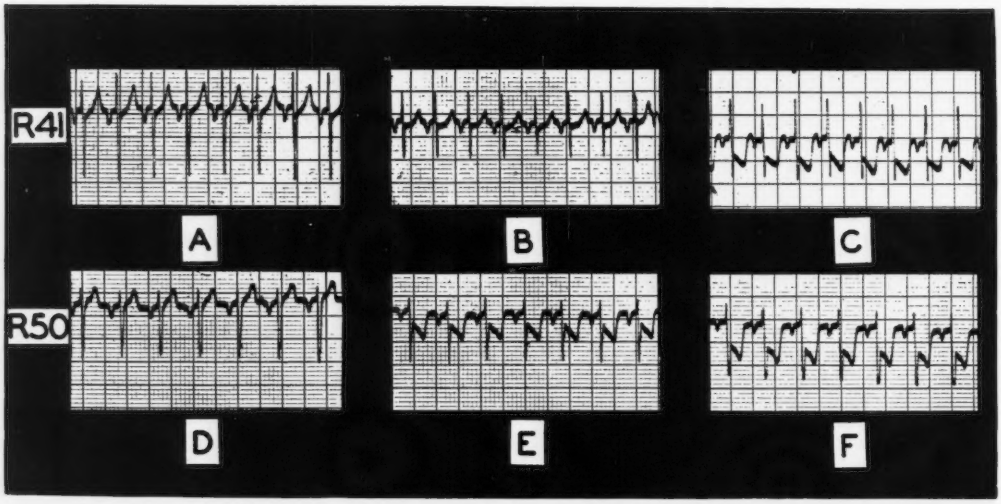

FIG. 2. Electrocardiograms taken on lead aV_R. *A*. control; *B*. 1½ minutes after coronary sinus arterialization at 50 mm. Hg; *C*. same but 1 minute after ligation of circumflex artery; *D*. control from control dog; *E* and *F*. changes produced in 30 seconds and 1 minute respectively following circumflex artery ligation without previous sinus arterialization.

These changes consist of marked T wave inversion, S-T segment displacement and increased amplitude of the QRS complex in aV_R. That these electrocardiographic abnormalities are similar to those occurring without sinus arterialization may be seen by comparing figure 2 *C* with figure 2 *E* and *F*, the latter two records being taken from a control dog.

A study of table 1 reveals that the one constant difference between the two groups was the mean aortic pressure decline of 12.7 mm. Hg which resulted from arterialization of the coronary sinus.

Discussion

A statistical analysis of the mortality rates in these experiments shows the 100 per cent survival in the arterialized group of 10 dogs to be highly significant. When calculated for differences in the B group the significance value is .0015. If the total group of 20 control dogs is compared with the arterialized group the value is less than .0015. This means that the chance of 10 consecutive dogs to survive acute circumflex ligation is about 1 in 667. The rather small differences in average values shown in table 1 in regard to dog weight, arterial oxygen content, coronary sinus arteriovenous oxygen difference, aortic pressure and per cent of total heart rendered ischemic would indicate that the groups were similar. All the dogs were operated in the same manner and in the same experimental time. The circumflex arteries were all ligated at the same location, namely, at their origins. This in all cases included the left auricular artery which in many cases produced auricular arrhythmias. We believe, therefore, that these experiments critically demonstrate that in dogs acute arterialization of the coronary sinus at a pressure of 50 mm. Hg protects the hearts from ventricular fibrillation after acute circumflex artery ligation.

These experiments answer certain questions. First of all, they demonstrate convincingly that this procedure is immediately effective and therefore must depend upon existing vessels and not the growth of new vessels. Second, these studies rule out the possibility that the protection induced by this procedure results from the growth of extra coronary collaterals through scar tissue. Finally, the severe electrocardiographic abnormalities in all dogs after circumflex arterial ligation show without doubt that arterialization of the coronary sinus does not even approximate the original function of the occluded artery. The fact that the ischemic area is dark in color and is seen to bulge with systole lends support to this view. Nevertheless these hearts continue to beat and usually maintain adequate levels of blood pressure. At present we have no positive information on the possible changes in cardiac output.

This study raises immediate questions as to the mechanism of the observed protection. In the first place, does the presence of such an arteriovenous fistula so close to the heart, with the observed average fall of 12.7 mm. Hg in aortic pressure, in itself modify the mortality rate after coronary arterial ligation? Second, will simple elevation of coronary sinus pressure without the arterialization of the sinus likewise protect against ventricular fibrillation? That this is possible is strongly suggested by the studies of Gross,[6] who was able to reduce the incidence of ventricular fibrillation and myocardial infarction following ligation of the left descendens artery by previous partial ligation of the coronary sinus. Finally it must be suggested that this procedure may even embarrass the capillary circulation in the areas of the heart supplied by the nonligated vessels, thereby reducing cardiac output work and oxygen requirement. Such a possibility suggests itself because of observations on the resistance to ventricular fibrillation which is seen in dogs with low outputs due to long periods with open chests. It is clear that these possibilities must be studied. Experiments are already in progress and will be reported in the near future.

Summary

Acute mortality rates have been determined in 30 dogs following acute circumflex artery ligation. In 10 of these dogs the coronary sinus was arterialized at a pressure of 50 mm. Hg immediately prior to the arterial occlusion.

There was a 70 per cent mortality within one hour in the 20 control dogs without arterialization of the sinus while there were no deaths within one hour in the experimental group of

10 dogs with arterialization of the sinus. A statistical analysis shows these mortality differences to be highly significant.

It is suggested that arterialization of the coronary sinus in dogs protects them from ventricular fibrillation following circumflex arterial occlusion, but such a procedure is by no means a total substitute for the function of the occluded vessel.

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We are indebted to Miss Nena Pero and Miss Martha McClaren for the analysis of blood samples for the oxygen content.

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Graphic Representation of Electrocardiographic Leads by Means of Fluid Mappers

By Richard McFee, M.S., Robert M. Stow, M.D., and Franklin D. Johnston, M.D.

A new method for the study of electrocardiographic leads is described. It makes use of plaster models having the same shape as the body in the frontal (or other) planes through which water flows in sheets. The flow of water is approximately analogous to the flow of electric currents through the body, and the flow lines are made visible by small crystals of soluble dye. If fluid passes in and out of the flow space from points that correspond to the location of electrodes of the electrocardiographic leads, the flow lines may be used to study the effects that electromotive forces arising in the heart have on these leads. With these models it is possible to study many different kinds of leads and the effects of variations of body shape, position of the heart, and electric conductivity of the tissues on them. Preliminary observations largely concerned with standard, unipolar extremity and chest leads are reported.

THE STUDY of electrocardiographic leads is not easy, because the body is a very complex conductor and the electric field within it is difficult to predict and visualize. The more or less mathematic approaches which have been made to the problem in the past have not been well understood by most cardiologists because of the mathematics, and not acceptable to others because of the relatively gross assumptions upon which the theories are based. In this paper we present a new method for investigation of electrocardiographic leads which makes use of simple laboratory instruments called fluid mappers. These are hydraulic models made with the same shape as the body and are arranged so that the resistance to the flow of fluid in them is analogous to electric resistance to current flow within the body. Fluid mappers require no mathematic background to build or operate, and for this reason we feel that this paper will be of interest to many cardiologists.

We believe studies with fluid mappers are important because they provide a simple method of obtaining graphic representations of various types of electrocardiographic leads and of visualizing the relations between the voltages recorded in them and the electromotive forces generated in different parts of the heart. The flow patterns seen in the mappers not only give a great deal of insight into the meaning of the leads, but also make it possible to estimate in a simple manner the errors involved in various electrocardiographic hypotheses including those upon which the Einthoven triangle and the central terminal for obtaining unipolar leads are founded.

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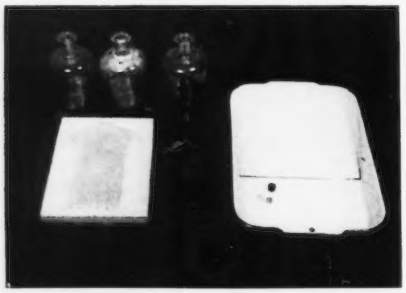
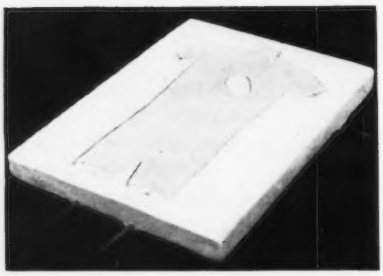
Method

The first fluid mappers were constructed by Hele-Shaw and Hay[1] in 1904 and were used to study electric and magnetic fields, having a two dimensional character. Their work was based on mathematic studies which indicated that there is a close analogy between such fields and the flow of fluids in plane sheets. The experiments of Hele-Shaw and Hay verified the accuracy of this theory, but their technic was so complicated that the method never came into widespread use. Moore[2, 3] in

1949 revised and greatly simplified the procedure with the introduction of his plaster of Paris fluid mappers. He showed how these simple and easily constructed devices may be used to study problems not only in connection with electric and magnetic fields, but also in relation to chemical diffusion and heat flow. Fortunately, we went to Professor Moore for advice, and it was in our conversations with



A



B

FIG. 1. *A*. View of a fluid mapper and all equipment needed for the operation of the devices. *B*. Detailed view of the same mapper shown in *A*. The model shown in both figures has the region of the heart milled out, corresponding to a heart of greater conductivity than the surrounding tissues.

him that the possibility of using fluid mappers to study electrocardiographic problems arose. In our use of fluid mappers, the flow of fluid simulates the flow of electric current in the body.

A fluid mapper consists of a plaster slab about 8 inches wide, 11 inches long, and $\frac{3}{4}$ of an inch thick, with plaster barriers an inch or more wide and $\frac{1}{16}$ of an inch thick along the edges. These barriers are made so that the region inside of them (the flow space) is of any desired outline, for example, that of the human body in the frontal or any other plane. A glass plate rests snugly on the barriers, and when the mapper is in use, water flows between the glass and the slab from sources to sinks (points of exit) that are located at points that correspond to sites of electrodes used to take electrocardiographic leads. The paths of the flow of water are made visible by crystals of potassium permanganate or methylene blue sprinkled on the plaster surface or glued to the under surface of the glass plate. The resistance to the flow of fluid (and this is analogous to the electric resistance of the tissues within the body) may be increased or decreased in any desired part of the model by raising or lowering appropriate areas of the plaster surface. Several views of a fluid mapper are shown in figure 1. The details of construction and operation are described in two very lucid, nonmathematic papers by Moore[2, 3] and will not be repeated here.*

THE RELATIONSHIP BETWEEN FLOW LINES SEEN IN FLUID MAPPERS AND ELECTROCARDIOGRAPHIC LEADS

Before the results of our studies with fluid mappers are presented, a few words to explain why these devices are so useful in the study of electrocardiographic leads are in order. The flow lines made visible by crystals of dye in the mappers are approximate representations of lines of current flow in the body that would exist if a battery were connected either directly or indirectly through equal resistances to electrodes at points on the body that correspond to the sources and sinks (points of exit) of fluid in the mappers. At this point the critical reader may object, since he has observed that the sources for flow lines (either fluid or electric) are located at points that correspond to the sites for electrodes of electrocardiographic leads, and are not within the heart. In other words, the situation actually existing in the human body has been reversed. Therein lies much of the value of the method, and its use may be completely justified by the reciprocity theorem of Helmholtz. In its simplest form this theorem states that in any passive electric network made up of resistances connected to a battery and an ammeter, the current recorded by the latter will remain the same when positions of the battery and the ammeter are

* Mimeographed instructions describing in detail the procedure we have used in the construction and operation of the mappers will be sent on request.

interchanged. In the case of the system formed by an electrocardiographic lead and the body, this theorem implies that *when the electromotive forces within the heart are directed perpendicularly to the flow lines, they will produce no voltage in the lead, and when they have the same direction as the flow lines they will produce a maximal effect.** To see how this simple principle is useful, consider the usual interpretation of lead I. This lead is supposed to be insensitive to electric forces within the heart, directed along the long axis of the body. If this is so, all flow lines resulting when lead I is connected to a source of current should pass through the heart horizontally, in the fashion shown in the upper right drawing in figure 5.

If all of the assumptions upon which the Einthoven triangle is based are assumed to be true, the flow patterns for the standard and unipolar extremity leads shown in the column on the right of figure 5 will be found. In the case of unipolar chest leads it can be shown that the flow lines within the heart should appear to radiate out from the exploring electrode on straight lines. The rigorous derivation of these ideal flow patterns and the principles used to interpret the flow lines will be given in another paper.

Results

Standard and Augmented Unipolar Leads

Three different models were used for studying these leads. The first corresponded to an electrically homogeneous body, and the second to a body in which the heart had about one-third the resistance of the other tissues. The third represented a body where the lungs and liver had nearly four times the resistance of the other tissues. In the second model the relative resistivities were approximately those found by Kaufman and Johnston,[4] while the third was based on the same assumptions Burger and von Milaan[5] used in their "Phantom.' The shapes of the first two models were identical, while the third had a somewhat shorter trunk.

Figure 2 shows "lead I" with the model of the first type. The fluid enters the right arm and leaves from the left. Figure 3 shows "lead III" with the model of the second type. This model is exactly the same as the previous one, except that the area of the heart has been milled out $\frac{1}{32}$ of an inch, thus making the flow space 50 per cent deeper in this region. This decreases the effective resistance of the heart to about $\frac{1}{4}$ of that existing in other regions within the mapper.* Methylene blue crystals were glued to the under surface of the glass and water flowed in from the left leg and out through the left arm when the photograph reproduced in figure 3 was taken. Fig-

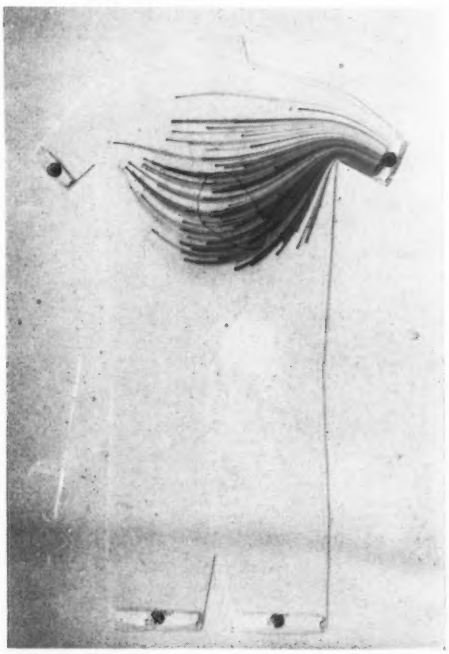


Fig. 2. Flow lines that depict standard lead I, taken with a model that represents the body as a homogeneous conducting medium. Here water entered the flow space from the right arm and passed out from the left arm.

* More specifically, if a current is introduced into any lead, the resulting current density at any point in the heart will have the same direction and relative magnitude as the Burger "lead vector" for electromotive forces at that point.

* The effective flow resistance in the mappers varies inversely with the cube of the depth of the flow space.

ure 4 shows "lead aV_F" with the model of the third type. Here the flow space in the areas of the lungs and liver was decreased by 33 per cent, thus increasing the effective flow resistance about four times. Methylene blue dye was also used here, and special precautions were taken to insure that the water, entering by the leg, left the flow space at equal rates from the two arms of the model.

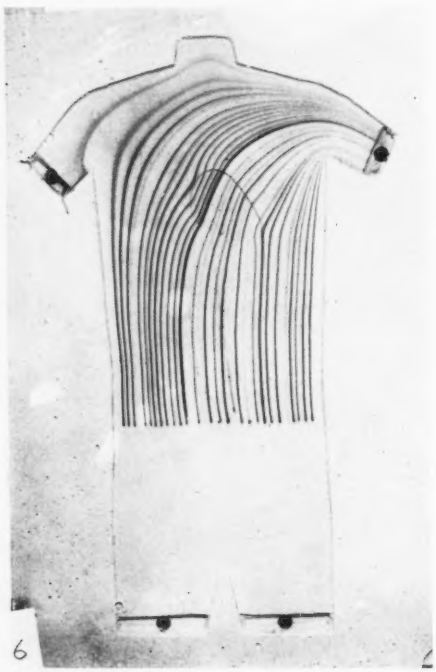


FIG. 3. Flow lines that illustrate standard lead III taken with the mapper shown in figure 1. Here the heart has greater conductivity than other tissues and fluid passed from the left leg to the left arm.

All the information obtained with these models is presented together in figure 5. Since we are only interested in the flow lines passing through the heart, this figure shows the lines in that region only. Six leads, the three standard leads and the three augmented unipolar extremity leads, are shown for each model. In order to facilitate direct comparison, the flow lines which would exist if all the hypotheses underlying the Einthoven triangle were fulfilled are shown in the fourth column.

Inspection of figure 5 makes it clear that the flow lines through the heart found in various leads with the fluid mappers are similar but not identical to those obtained by use of the Einthoven triangle concept. We think that these results support the view that the Einthoven triangle theory is accurate enough for most clinical purposes. It is of considerable interest that, in the mappers made to reflect

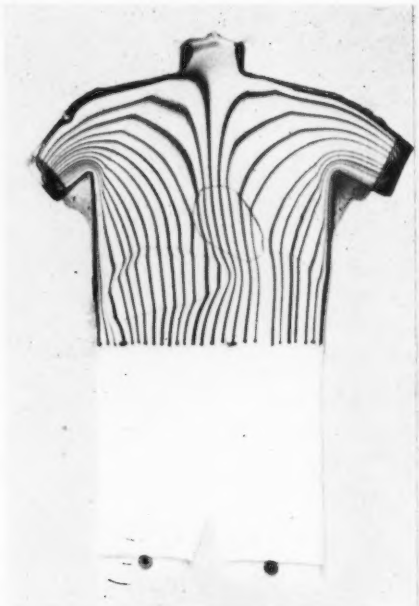


FIG. 4. Flow lines that represent lead aV_F taken with the model built to behave like a human body with lungs and liver of higher resistance than other tissues. Here fluid entered the flow space from the left leg and passed out in *equal* amounts from the two arms.

fairly closely the variations in electric resistance in the body, the flow lines passing through the heart are straighter than are those seen in models corresponding to a homogeneous conducting medium. This suggests that differences in tissue resistances may act to minimize, rather than increase, one type of error involved in the use of the Einthoven triangle.

Chest Leads and the Central Terminal

The interpretation of the standard and unipolar limb leads in terms of a manifest vector,

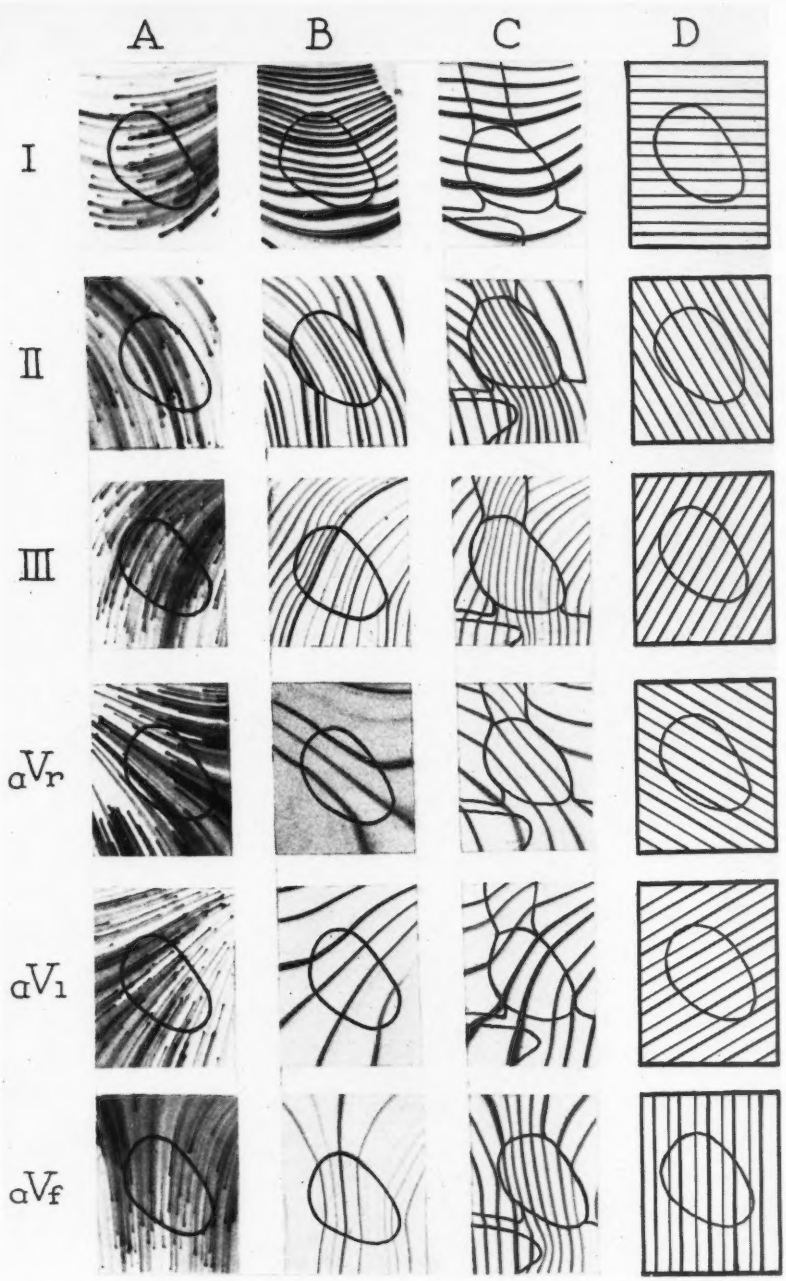
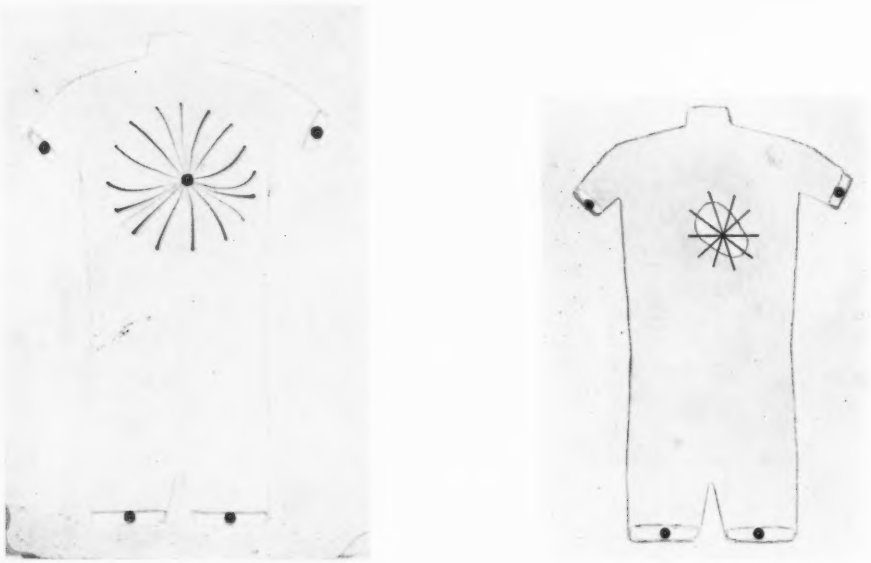


FIG. 5. Composite figure showing flow lines, in the region of the heart only, representing the three standard and unipolar extremity leads taken with three different mappers. Those in column *A* correspond to a body that is a homogeneous conducting medium, those in column *B* to a body with a heart of greater conductivity, and those in column *C* to a body with lungs and liver of lower conductivity (higher resistance) than other tissues. The drawings shown in column *D* illustrate the type of flow lines that would exist in the heart if all of the hypotheses, upon which the Einthoven triangle theory is based, were strictly true. It should be pointed out that, in these drawings, the flow lines outside of the heart need not be parallel and of the same direction as those within the heart. (See text.)

and of the unipolar chest leads in terms of a potential measured to an "indifferent" point, follow logically from the same set of assumptions. For this reason one would expect that studies which deal with the limb leads would also have bearing on the chest leads, and vice versa. Although this is doubtless the case, different combinations of electrodes are employed when the limb and chest leads are taken, and experiments designed to depict the latter, as well as the former, are clearly desirable.



A *B*

FIG. 6. *A*. Flow lines that represent a mid-precordial lead taken with the central terminal as the indifferent electrode. Here fluid passed into the flow space in *equal* amounts from the right arm, left arm and left leg and out through the orifice in the heart. The model used corresponds to a body with a heart of greater conductivity than the other tissues. *B*. Lines drawn from heart of model to represent idealized perfect unipolar lead. Note great similarity between *A* and *B*.

It was pointed out previously that if the central terminal is a truly "indifferent" point, then a source of current connected to an exploring electrode and to the central terminal should produce flow lines within the heart which radiate from the exploring electrode in a symmetric radial fashion. Figure 6 shows the flow lines produced when an experiment testing this was done. Here water flowed in at equal rates from the three limbs and out from the center of the heart. The mapper used here was one with a deeper flow-space over the region of the heart, corresponding to a heart with greater conductivity than the other tissues. The radial spread in the region of the heart shown by this figure closely approximates the pattern which would exist if all of Einthoven's assumptions were true, thus supporting the use of the central terminal as an indifferent electrode. Figure 6 should be compared with figure 7, which illustrates the assymetric and curved flow-lines seen in the same model when it is arranged to simulate the CF lead. Here, of course, fluid passes only from the left leg to the heart.

Several other models of different kinds, including some representing flow lines in a sagittal plane, have been used to study chest leads. These also show that when the central terminal is used the flow patterns within the heart correspond fairly well to the theoretic pattern for an "indifferent" electrode, and that this is

not the case when other points are chosen as reference electrodes. It was found with these models that the radial spread of the flow lines within the heart was not appreciably changed when the latter was given a lower resistance than the rest of the body, although the field outside the heart was altered considerably. In addition, these studies indicate that even a

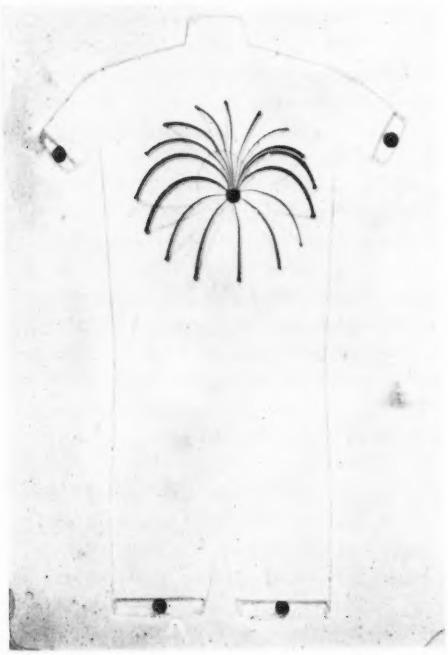


FIG. 7. Flow lines that represent a mid-precordial lead with the left leg as the indifferent electrode. The same model was used as in the experiment illustrated in figure 6. To obtain this CF lead fluid entered from the left leg and passed out through the orifice in the heart.

thick layer of subcutaneous fat (offering high resistance to current flow) does not alter the flow lines through the heart greatly, thus suggesting that the interpretation of precordial leads is not influenced a great deal by the character of the subcutaneous tissues. Figure 8 illustrates the situation just mentioned. The lines are refracted as they pass through the portion of the model representing the subcutaneous fat pad, but the pattern of flow through the heart itself is not significantly changed.

It should be pointed out that the radial spread of the flow lines found in all of these models indicates that chest leads are most sensitive to electromotive forces in parts of the heart close to the exploring electrode. This means that the potentials measured by these leads will not, in general, be the same as they

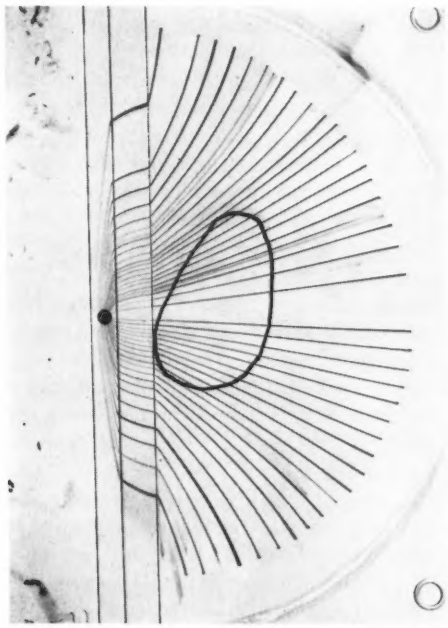


FIG. 8. This figure shows flow lines in a model built to represent the body in a sagittal plane, with a raised barrier analogous to a thick subcutaneous fat pad under the exploring electrode. Refraction of flow lines in this region is evident, but the course of the lines passing through the heart is nearly the same as it would be if the fat pad were absent. Fluid entered the flow space here from a semicircular channel, corresponding to an indifferent electrode at infinity, and passed out through the orifice that represents the exploring electrode.

would be if all the electromotive forces in the heart were located at its center, or in other words will not be strictly proportional to the component of the mean cardiac vector in the direction of the electrode.

DISCUSSION

The graphic representations of the various leads shown in our figures illustrate a number

of important principles of electrocardiography. It will be noted that the current lines converge or diverge strongly near the regions of entrance or exit but are more nearly straight and parallel midway in their course. For this reason, when the heart is far from both lead electrodes the deflections produced by electromotive forces arising in different parts of the heart but having the same magnitude and direction will be nearly the same. On the other hand, when the heart is far from one electrode and close to the other, the lines will tend to crowd into the part of the heart close to the latter. This, of course, will make the lead more sensitive to electromotive forces in the portion of the heart closest to the nearby electrode.

Careful study of the figures shows that refraction of the flow lines always occurs with a change in the resistance of the medium through which they pass, in a fashion analogous to the refraction of light rays. This refraction is just one aspect of the over-all change in the flow pattern which results when the resistance of one part of the model is made different from the rest. Sometimes the end result is quite surprising, as it is in the model representing the heart of higher conductivity. Here the lines within the heart become more nearly parallel in spite of their sharp refraction at the boundaries of the heart.

If the conductivity of the heart is greater than that of its surroundings, the flow lines will crowd into it, and the deflection produced by a double layer electromotive force having a constant potential difference will usually be greater than it would be if the heart had the same conductivity as the tissues around it.

The use of fluid mappers in the solution of analogous electric problems in the human body is based on the assumption that the tissues of the body are resistive conductors. For high frequency alternating currents this would not be true, but studies of our own, as well as those of many other investigators, demonstrate that at the rather low frequencies involved in electrocardiograms these tissues may be considered to be pure resistances.

All of the studies which we have done thus far have indicated that the general character of the flow lines through the heart is not influenced appreciably by variations in the resistances of the tissues outside of it. It is possible, however, that changes of resistance within the heart may alter the lines therein but, in any case, mappers may be constructed for the study of this situation. Plateaus and depressions in appropriate parts of the heart would simulate variations in resistance from one region to another, and parallel grooves in the plaster would produce an effect similar to variations of electric resistance with change in the direction of current flow.

One cannot expect fluid mappers to give reliable information unless the plaster slabs are carefully and accurately made and the experiments using them performed with care. When we have followed these precautions, we have been able to reproduce closely flow lines representing certain leads with different mappers. Leakage across the barriers surrounding the flow space has been our most troublesome problem, and it can be prevented only by careful application of a thin layer of stopcock grease on the under side of the glass plate, where it rests on the barriers.

Two dimensional devices such as the fluid mapper cannot, of course, give direct solutions to three dimensional problems such as those encountered in the body. The chief value of the mappers lies in their ability to depict flow lines associated with different kinds of leads in a simple manner and in the quick and easy manner by which they give insight into difficult problems. We feel that they may be particularly useful in the qualitative study of the effects that changes in body contour, variations in resistance of the tissues, and shifts in the position of the heart may have on the various leads.

The studies reported here are only preliminary, and the effects of all the variables just mentioned have not been adequately investigated. Further studies with fluid mappers may make it possible to devise new leads with which the components of the heart vector in the various planes can be measured more accurately than is now possible. The need for improved technics of this kind, particularly in the field of spatial vectorcardiography, is clear.

Summary

1. A simple new method for the experimental study of electrocardiographic leads is described. This involves the use of plaster slabs constructed so that water flows in a narrow space which has the outline of the body as seen in the frontal or other planes. The flow space is covered by a glass plate and the fluid enters and leaves from orifices which are located at points analogous to those of electrocardiographic electrodes. Fluid flow-lines through the heart or other parts of the model are made visible by crystals of potassium permanganate or methylene blue placed on the plaster surface or cemented to the undersurface of the glass plate. Variations in resistances of tissues within the body may be simulated by varying the depth of the space where the water flows within the mapper.

2. The flow lines shown by the fluid mappers have the same directions that electromotive forces at various points in the heart must have in order to produce a maximal voltage in the lead. Electric forces perpendicular to these lines will contribute nothing to the lead voltage.

3. The character of the flow lines in mappers representing standard and unipolar leads suggests that the Einthoven triangle concept is satisfactory for general clinical use and that the central terminal is a good indifferent electrode. Furthermore, it appears from these studies that a heart of lower, or lungs and liver of higher, resistance may act to increase the accuracy of these theoretic propositions rather than the reverse.

4. Fluid mappers provide a powerful new tool for the study of electrocardiographic leads and aid greatly in an understanding of their meaning. Further studies with these simple hydraulic models may lead to the development of new leads which are superior to those now available not only in the frontal but other planes as well.

Acknowledgements

The authors wish to express their indebtedness to Professor A. D. Moore. His industry and ingenuity have developed fluid mappers to the point where they are useful in many fields, and his suggestions have helped us greatly in the construction and operation of the mappers we have employed. Dr. Frank N. Wilson has encouraged us to carry out this work and has aided us a great deal in the preparation of the paper. We are deeply grateful for his unfailing support.

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Orthostatic Hypotension, Anhidrosis, and Impotence

By MARVIN ROSECAN, M. D., ROBERT J. GLASER, M. D., AND MELVIN L. GOLDMAN, M. D.

Anhidrosis and impotence occur frequently with idiopathic orthostatic hypotension. Two new cases of this syndrome, which occurs chiefly in males over 40 years of age, are herewith described. Postural vertigo and/or syncope, weakness, and anhidrosis or hypohidrosis are common symptoms, and a marked fall in systolic and diastolic blood pressure is noted when the patients stand. The pathologic physiology of the syndrome is discussed and various forms of therapy, none of them especially satisfactory, are reviewed.

IN 1925 Bradbury and Eggleston[1] reported the occurrence of a hitherto unrecognized clinical phenomenon, orthostatic hypotension, which they observed in three males, all of whom sustained a fall in systolic and diastolic blood pressure when they assumed upright posture. Their patients also exhibited a slow, unchanging pulse rate, dizziness, syncope, and anhidrosis or hypohidrosis. Subsequently, many instances of postural or orthostatic hypotension have been reported. In general, two types may be defined: (1) those due to known cause, among which are sympathectomy,[2] tabes dorsalis,[3–10] diabetes mellitus,[3, 11] myasthenia gravis,[12] Addison's disease,[7, 13, 14] hypopituitarism,[15] syringomyelia and hematomyelia[3]; and (2) those due to unknown or ill-defined disease of the central nervous system. In the latter group of patients a wide spectrum of signs and symptoms has been observed, but the findings in some of the patients cannot be considered to conform to the clinical syndrome originally described by Bradbury and Eggleston. For purposes of this study arbitrary criteria have been established to emphasize the concomitant occurrence of postural hypotension, anhidrosis and impotence a triad to which attention was first called by East and Brigden.[16] Only those cases, therefore, manifesting significant systolic and diastolic postural hypotension,* with an unchanging or only slightly increased pulse rate, and anhidrosis or hypohidrosis have been included. With the two cases which we have observed and which are herein described, a total of 37 cases[1, 4, 5, 16–41] has been gathered from the literature.

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CASE REPORTS

Case 1. E. W. (B. H. 182971),† a 65 year old white married painter, was admitted to the Barnes Hospital for the first time on April 1, 1950, for study of "low blood pressure." His chief complaints were dizziness and lightheadedness of two years' duration. Three years before entry he noted that he ceased sweating on the left side, and one year before entry he stopped perspiring on the right side. Two years before admission he also began to feel "lightheaded" whenever he stood up. Concomitantly dizziness appeared when he was erect, and he had a rather sudden lapse of sexual desire and potency. About one year before entry he consulted a physician who told him that his blood pressure was 140/70 when he was sitting, but 60/40 when he stood up. Aside from slight dyspnea on exertion he had no other immediate complaints.

The past history revealed that the patient had had gonorrhea at age 23, and syphilis at 51. For the latter disease he was treated with 18 injections of an arsenical compound, and subsequently four serologic tests were negative. He had never had a lumbar puncture. Five years prior to entry he had transient nocturnal diarrhea. His weight had been quite constant for several years. His skin had always been rather dry.

The patient had been married three times. Until

* A fall in blood pressure of at least 35 mm. Hg systolic and 20 mm. Hg diastolic was considered to be significant.

† Referred by Dr. James Allee, Columbia, Mo.

the rather sudden onset of loss of libido and the development of impotence two years before, he had continued to have intercourse frequently, usually once or twice a week. He had worked as a painter for many years.

Physical examination at the time of entry revealed the patient to be an obese white man who did not appear ill. His temperature was 37 C. The blood pressure in the arms, with the patient recumbent, was 120/65 mm. Hg; with the patient recumbent but with his legs elevated, the reading was 150/90 mm. Hg. When he stood his blood pressure fell to 84/40 mm. Hg. The pulse remained constant at 80 during all of these determinations. The skin was extremely dry and rather scaly, particularly on the hands and forearms. The axillas were slightly moist. The left pupil was round, the right somewhat elliptical, but both reacted well to light and accommodation. Physical examination was otherwise entirely negative.

Laboratory data included a normal hemogram. The urine and stool examinations were negative as was the blood Kahn test. The nonprotein nitrogen was at the upper limit of normal; the fasting blood sugar was normal. An electrocardiogram was normal except for low voltage. The circulation time with Decholin was 17 seconds with the patient recumbent and 30 seconds when he was standing. Two basal metabolic rate determinations were −13 and −16 per cent respectively. Urinary gonadotropin excretion in 24 hours was 8.7 mouse units, a normal value.* The cerebrospinal fluid was normal.

When a heat cradle was applied over the trunk for thirty minutes only slight sweating in the axillas, inguinal areas, and over the sternum resulted. After administration of 10 mg. of pilocarpine subcutaneously much more sweating was noted in all areas of the body. Only a slight subjective sensation of palpitation was produced by the subcutaneous injection of 0.6 mg. of epinephrine. There was no actual rise in blood pressure or pulse rate, and the postural hypotension was unaffected. The pulse rate did not increase when 0.6 mg. of atropine was given subcutaneously. The blood eosinophile response to epinephrine was within normal limits.

The cardiac output, as estimated by the tilt table ballistocardiograph,† did not show a significant decrease when the patient was tilted 45 degrees from the horizontal; his pulse rate remained constant.

A summary of the effects of various drugs upon blood pressure and pulse is given in table 1.

Ephedrine in doses of 25 mg. did not benefit the patient significantly. When ephedrine was given in doses of 50 mg. by mouth, and the patient's legs were kept wrapped tightly with elastic bandages, more improvement resulted than with any of the many other therapeutic measures attempted. Therefore, the patient was discharged on April 7, 1950, and advised to take 50 mg. of ephedrine after each meal and 25 mg. before retiring. In addition, he was instructed to wrap his legs daily with elastic bandages.

Follow-up Note. The patient was seen briefly about one month after discharge at which time his condition was essentially unchanged. Two weeks later, after returning to his home, he expired rather suddenly. Unfortunately, he was not seen by a physician and an autopsy was not performed.

Case 2.—D. F. (B. H. 84006), a 62 year old white married miner, was admitted to the Barnes Hospital for the fifth time on March 1, 1949, complaining of "fainting spells." The past history was of interest only in that the patient had been constipated for many years.

Twenty-three years before entry, at the age of 39, the patient developed increasing fatigability, weakness, and dizziness on standing. These symptoms persisted until entry, and had become so severe that when he stood up he lost consciousness. Approximately at the same time that the previous complaints began, the patient noted relative impotency which likewise progressed so that he was soon unable to indulge in sexual activity. Sixteen years before entry he became aware that he sweated less than his fellow workers in the coal mine and that the heat seemed to bother him more than the other men. Concomitantly he also had frequent temperature elevations. In the ensuing 16 years there was a progressive decrease in sweating so that by the time of admission the patient had almost completely ceased perspiring.

He first entered the Barnes Hospital in August, 1940, at which time his blood pressure was found to be normal when he lay recumbent, but it was observed to fall precipitously when he stood up, levels of the order of 60/40 mm. Hg being recorded. During his first admission he was studied with the possibility of Addison's disease as the prime consideration, but that diagnosis was not confirmed and he was discharged with a diagnosis of idiopathic hypotension. He subsequently was readmitted four times. Each time he was found to have persistent postural hypotension without evidence of other disease. His temperature was frequently slightly elevated.

In the year prior to his last admission the patient had had progressive increase in weakness and ease of fatigability; he had been unable to drive a car because of blurred vision. During the four weeks prior to entry he fainted on three or four separate

* This determination was made in the laboratory of Dr. Willard M. Allen, Department of Obstetrics and Gynecology, Washington University School of Medicine.

† The authors are grateful to Dr. Arthur E. Gropper who performed the ballistocardiography.

occasions, and on one of these was unconscious for three hours.

Physical examination at the time of entry revealed his temperature to be 37 C., pulse 76, respirations 18; the blood pressure was 95/60 mm. Hg with the patient recumbent, 75/60 mm. Hg when he sat erect, and 60/0 mm. Hg when he stood. While the erect blood pressure was being determined the patient fainted. His skin was dry and scaly, and he did not perspire. The remainder of the examination was negative.

toe as well as in the pinna of the right ear lobe was recorded by photoelectric plethysmographs.[42] The patient was then tilted 20 and 45 degrees from the horizontal. The blood pressure fell from 156/80 mm. Hg in the horizontal position to 87/63 mm. Hg at a 45 degree tilt. The pulse rate was 72 per minute with the patient horizontal and increased to only 84 when he was tilted. The subject complained of dizziness and began to black out after 45 seconds in the tilted position. The amplitude of the plethysmographic tracings decreased, suggesting either (1)

TABLE 1.—*Effect of Certain Drugs on the Blood Pressure in Two Patients with Idiopathic Orthostatic Hypotension*

Subject	Drug	Dose *mg.*	Route of Administration*	Time of Reading Minutes	Position of Subject†	Blood Pressures mm. Hg	Pulse Rate per Minute
E. W.	Control	—	—	—	H	120/75	92
					U	80/40	92
					D	150/90	92
	Epinephrine	0.6	S.C.	30	H	120/75	97
					U	70/40	100
	Ephedrine	25	oral	120	H	130/80	84
					U	70/50	84
	Atropine	0.6	S.C.	15	H	105/75	84
					U	65/40	84
D. F.	Control	—	—	—	H	120/72	72
					U	60/50	90
	Epinephrine	0.5	S.C.	30	H	140/78	88
					U	70/50	104
	Ephedrine	45	I.M.	10	H	124/70	80
					U	63/50	116
	Benzedrine	10	I.M.	30	H	150/90	60
					U	65/54	100
	Paredrine	20	I.M.	30	H	168/100	72
					U	90/74	81
	Prostigmine	0.5	S.C.	15	H	152/94	64
					U	68/52	86
	Atropine	0.1	I.M.	30	H	98/70	94
					U	50/38	110

* S.C. = Subcutaneously
I.M. = Intramuscularly

† H = Horizontal Position
U = Upright Position
D = Head Down Position

The laboratory data included a normal hemogram. The urine showed a trace of albumin and many white cells per high power field in the centrifuged sediment. The blood Kahn test was negative. The nonprotein nitrogen was at the upper limit of normal; the fasting blood sugar was normal. The basal metabolic rate was −13 per cent. A chest film was interpreted as showing a tortuous aorta; the heart was normal in size and contour. An electrocardiogram was within normal limits.

The following special study was performed: the arterial blood pressure in the right brachial artery was measured by a Hamilton optical manometer while the blood flow in the right middle finger and

vasoconstriction and/or (2) decrease in blood flow in the peripheral parts. The records indicated a marked fall in the total blood volume of the ear lobe and only a moderate fall in the finger and toe.

The response of the patient's pulse and blood pressure to various drugs is summarized in table 1. It is of interest that 10 mg. of pilocarpine by the subcutaneous route produced generalized sweating.

The patient was discharged from the hospital on March 15, 1949, and was advised to take Prostigmine, 10 mg., three times daily.

Follow-up Note. The patient was seen about 15 months after discharge at which time his condition was essentially unchanged.

Occurrence

The patients with this syndrome have ranged in age between 39 and 72 years, the average being 53. Males have outnumbered females by a ratio of four to one. Occupational factors have not been obvious although it is of interest to point out that there had been significant contact with paint[18] or heavy metals[16] in two of the previously reported cases, and in one of the two added herewith. In all three of these patients the signs and symptoms of the syndrome were advanced.

Symptoms*

The onset of symptoms in the earliest case occurred in a patient 23 years of age, and the latest onset was noted in a man aged 63. The most pronounced symptoms were postural vertigo, syncope, weakness, blurring of vision and loss of mental acuity prior to syncope. On the other hand syncope usually developed without premonitory nausea, pallor, or other vasoconstrictive aura. Symptoms were characteristically more severe in the morning when the patient first arose, after meals, exercise and in warm weather. In only one of the cases have convulsive seizures been noted[4]; in another patient voluntary shaking movements of the arm preceding the attack of syncope were described.[39]

Anhidrosis or hypohidrosis occurred in all 37 cases. Often anhidrosis was limited to only certain portions of the body,[5, 17, 26] and in several cases was unilateral at some time during the course of the patient's illness.[16, 26, 32] In still other patients only the lower half of the body was involved.† [19, 39]

Direct inquiry concerning impotence was made to only 18 male patients. Since it was present in 17 of them, it is probably much more common than previously appreciated. It was sudden in onset in several patients aged 30 to 50.[1, 4, 5, 16, 26, 32, 33, 37] Nocturia was present in 18 of 20 patients to whom specific inquiry was made in regard to this symptom. Bladder disturbances, such as incontinence, were recorded six times. Six patients were constipated, and four complained of diarrhea.

Table 2.—*Symptoms, Signs and Laboratory Findings in Idiopathic Orthostatic Hypotension*

	Number of Times Sought For	Number of Times Found	Per cent Found
Symptoms			
Postural vertigo or weakness	37	37	100
Postural syncope in addition	37	29	78
Anhidrosis or hypohidrosis	37	37	100
Impotence or loss of libido	18	17	94
Nocturia	20	18	90
Bladder disturbances	8	6	75
Diarrhea	11	5	45
Constipation	11	6	55
Signs			
Postural fall of systolic pressure 50 mm. Hg	37	30	81
Postural fall of diastolic pressure 30 mm. Hg	37	31	84
Postural fall to systolic pressure 70 mm. Hg or less	37	30	81
Postural increase in pulse rate of 10 per minute or less	36	23	64
Dry skin	20	12	60
Abnormal neurologic findings	37	14	38
Laboratory Findings			
Normal ECG	20	18	90
BMR −10% or below	23	14	61
Elevated NPN or BUN	21	15	71
Sweating induced with pilocarpine	14	14	100
Unchanging pulse rate after atropine injection	11	11	100

Signs

In most of the patients postural hypotension was marked. In 81 per cent of the cases a fall in systolic pressure of more than 50 mm. Hg was observed within a few seconds after the patient assumed the upright position, and the diastolic blood pressure fell 30 mm. Hg or more in 84 per cent of the cases. Sixty-four per cent of the patients showed a rise in pulse rate of less than 10 beats per minute. Carotid sinus

* A summary of the symptoms, signs and laboratory findings in idiopathic orthostatic hypotension is given in table 2; central nervous system abnormalities are shown in table 3.

† An extensive review of anhidrosis has recently been published.[43]

TABLE 3.–*Neurologic Abnormalities in Idiopathic Orthostatic Hypotension*

Report	Age and Sex	Memory Loss	Pupil Abnormalities	Increased Reflexes	Decreased Reflexes	Abnormal Toe Signs	Tremor	Nystagmus	Ataxia	Positive Romberg	Decreased Vibratory Sense	Adiadochokinesia	Relaxed Rectal Sphincter	Other Findings	Neurologic Diagnosis if any
Bradbury and Eggleston[1]	M67		Unequal	+	Bilaterally										
Moretti[34]	M65													Left VI nerve palsy.	
Granshorn and Horton[28]	M52			+ Legs		+ ? on R.	Intention tremor R. Arm	+	±	+	+			Ptosis of right eyelid.	
Chew and associates[5]	M53		Unequal										+		
Langston[39]	M56	+					+ Coarse							Emotional swings. Involuntary laughter prior to syncope.	
Baker[17]	M41		Left Horner's	+						+	+				Diffuse sclerosis of CNS
Ewert[40]	M67					+ R.								Bilateral ptosis. Left lower facial and palatal palsy. Tongue slightly to right. Interosseal atrophy in left hand.	
Jeffers and Montgomery[4]	M45		Sluggish	+ Legs		+ L.						+ Arms		Bilateral cerebral atrophy demonstrated by pneumoencephalograms.	
Laufer[32]	M49		Irregular Unresponsive		+ Absent in legs					+					Adie's syndrome
Hammarstrom and Lindgren[27]	M48	+	No light response on R. Decreased on L.	+ Ankle Clonus		+ L. and R.		+	+	+		+ R. arm	+	Slurred speech; apraxia. Cerebral atrophy demonstrated by pneumoencephalograms.	Diffuse areas of encephalomalacia
Young[41]	M43						+ Fine							Loss of tone of vocal cord. Masked facies. Flexion position.	Parkinsonism
Massee[38]	F60				+ Ankle		+ Fine		+	+				Possible Raynaud's syndrome in third finger.	
Nylin and Levander[18]	M69						Rest tremor L. side							Cogwheel rigidity in left arm.	Left-sided parkinsonism
Engel[37]	M54		Unequal		+ Legs			+							

pressure was generally ineffective in lowering the blood pressure or slowing the pulse rate. It is of interest that a degree of postural hypertension is also common in these patients; thus, raising the feet above the level of the heart frequently results in a distinct rise in the systolic and diastolic blood pressures.

Central nervous system abnormalities were present in 38 per cent of the patients. The findings were rather diverse, with abnormalities in pupillary reactions and reflex changes noted most often. Adequate criteria for definite neurologic diagnoses were present in only a few cases, but included in the clinical neurologic diagnoses were Adie's syndrome,[33] Horner's syndrome,[17] diffuse arteriosclerosis or atrophy of the central nervous system,[4, 17] and parkinsonism.[18, 41]

The skin was dry, coarse and scaly in 60 per cent of the patients in whom skin examination was specifically mentioned. No other consistent abnormalities in the physical findings were recorded.

Laboratory Findings

No particular deviations from the normal in regard to blood counts or urinalyses were noted. Of particular interest were the results of basal metabolic rate determinations. Approximately 60 per cent of the patients exhibited basal metabolic rates of −10 per cent or lower. All but two[32, 34] were in the range of 0 to −21 per cent.

An interesting negative finding was the fact that 18 out of 20 patients in whom electrocardiographic tracings were obtained exhibited no abnormalities. In the other two only minor variations from the normal were found. Two patients[4, 21] exhibited electrocardiographic changes during the episodes of hypotension and these consisted of inversion of T_2 and/or T_3. Electroencephalograms have been recorded in several patients and have shown no specific changes. In one instance, however, Engel[37] observed the electroencephalogram during an episode of postural syncope. He found changes which were typical of cerebral anemia and which have been described in other forms of syncope.

Most of the patients excreted large volumes of urine at night with a small diurnal volume of high specific gravity.[26] Decrease in phenolsulfonephthalein excretion,[1] creatinine clearance,[18] and urea clearance associated with a rise in blood urea nitrogen[16] was noted in several patients when they assumed the erect position. In addition some degree of nitrogen retention occurred in 71 per cent of the patients. In one a return of the nonprotein nitrogen level to within normal limits was noted after 10 days of bed rest.[23]

In patients with anhidrosis, the application of heat in various forms did not induce significant perspiration. Engel[37] noted also the absence of a shivering response in his patient. The injection of 5 to 10 mg. of pilocarpine subcutaneously produced marked generalized sweating in 14 patients.

There were normal blood pressure and pulse responses[44, 45] to the subcutaneous injection of 0.5 to 1.5 mg. of epinephrine in seven of nine patients. One was a hyper-reactor[26] who exhibited a marked increase in both the systolic and diastolic pressures. In no case was the degree of postural hypotension lessened. Our first patient was unique in that he had no increase in systolic blood pressure or pulse rate after 0.6 mg. of epinephrine subcutaneously. In none of the 11 subjects given atropine was there an increase in pulse rate.

Although normal subjects exhibit no increase in the arm to tongue circulation time when standing erect,[46] an increase was demonstrated in all patients with orthostatic hypotension subjected to the procedure.[3, 28, 32]

Course

In general there is little spontaneous fluctuation in the course of idiopathic orthostatic hypotension. Stead's first case[19] constituted an exception to this statement. The course usually is slowly progressive over a period of many years. One ominous note is sounded by the occurrence of sudden death in two of the three patients reported by Bradbury and Eggleston[1] and in our first patient, all of whom presented advanced examples of the syndrome. Other reported deaths were due to unrelated diseases.

Treatment

The therapeutic measures are of two types: (A), pharmacologic preparations, chiefly pressor agents; and (B), devices to increase blood volume.

A. *Pharmacologic Preparations.* In general large doses of vasopressor drugs are given early in the morning, the time when symptoms are usually most marked. These drugs often do not prevent pronounced postural hypotension but do afford considerable symptomatic relief in some cases. Their usefulness is limited by the nervousness, tremor, and insomnia which they produce. Ephedrine gave some relief in 18 of 24 cases, the doses ranging from 12.5 mg. once in the morning to 50 mg. every two hours.[5, 18] In isolated instances Neosynephrine,[21] Benzedrine[41] and Paredrine[24] were effective. A long acting preparation of norepinephrine might well constitute the most effective agent in the treatment of this disease.

B. *Measures to Increase Fluid Volume.* MacLean[35, 36] reported excellent results in patients when the head of the bed was elevated 20 degrees above the horizontal; the beneficial effects were enhanced by the administration of fluid and salt. An increase in circulating blood volume was demonstrated during treatment, and a relapse of symptoms occurred on cessation of therapy. Good results using similar methods were also obtained by Laufer[33] and by Corcoran.[47] The use of desoxycorticosterone acetate and a high salt intake in addition to vasopressor drugs has been reported to afford some symptomatic relief.[7, 21, 29, 48] Treatment with elastic leg bandage binders and abdominal belts has been generally unsuccessful,[31] although in our first patient, wrapping of the legs in combination with ephedrine was of some value.

Discussion

The pathologic physiology of postural hypotension has been studied by a number of investigators. Stead and Ebert[19] have convincingly demonstrated that there is pooling of no more than a normal amount of blood in the lower extremities of these patients. They have concluded that the cause of postural hypotension is an abnormal response to a normal shift in blood volume. Evidence is here reviewed that this abnormal response includes lack of arteriolar and venous constriction and absence of reflex tachycardia. In addition, there is in some cases a greater than normal fall in cardiac output.

Evidence for lack of vasoconstriction is gained from plethysmographic studies which demonstrate (a) absence of normal spontaneous changes in blood flow,[4] (b) absence of variations in blood flow with respiration or temperature,[19, 37] and (c) a greater than normal blood flow in the hand for a given fall in blood pressure.[19] That there is lack of arteriolar constriction, when a fall in blood pressure occurs, appears certain. However, it is not likely that arteriolar constriction is entirely absent in all cases. This statement is based upon the plethysmographic studies in our patient, D.F., the results of which are interpreted as indicating that although the vasoconstriction in the upper and lower extremities was not adequate to maintain cerebral blood flow, there was some degree of arteriolar constriction in these peripheral parts.

In our patient E. W., the cardiac output, as estimated by the tilt table ballistocardiograph, did not change significantly when the patient was tilted at an angle of 45 degrees, and the pulse rate remained the same. These findings are in agreement with those obtained in previous studies.[3, 49] On the other hand, in some cases[49] large degrees of postural hypotension were associated with greater than normal decreases in cardiac output, and under such circumstances, rapid infusion of albumin raised the cardiac output and blood pressure. These observations have been interpreted as suggesting that failure of normal venoconstriction may play a part in the decrease in cardiac output.[49]

Indirect evidence of failure of venous constriction in postural hypotension is obtained from the demonstration of a positive Flack test,[36] in which the subject, while in the erect position, blows into a spirometer with enough force to raise a column of mercury to a height of 40 mm. Normal subjects exhibit little or no change in pulse volume, as measured by the plethysmograph, during this procedure, while patients with postural hypotension become

pulseless within 10 seconds, and often syncopal, a result indicative of a decrease in venous return.

The physiologic response to hypotension includes reflex tachycardia. A failure of this response may be due to increased vagotonia or decreased sympathetic tone. The absence of an accelerating effect on the heart rate after adequate atropinization eliminates increased vagus tone as the factor responsible for the lack of postural hypotension. Since reflex control of vasoconstriction and sweating is mediated through the sympathetic nervous system, it may be assumed that the sympathetic nervous system is at fault. Stead and Ebert[19] and Nylin[18] have reviewed evidence which supports the hypothesis that the central and not the peripheral division of the sympathetic nervous system is involved.

Further evidence for a central lesion as the cause of the syndrome is gained from a consideration of anhidrosis. It has been observed that parenteral pilocarpine produces profuse sweating, but sweating does not occur when the external surface of the body is warmed. There is evidence that pilocarpine acts on the peripheral cholinergic fibers supplying sweat glands,[50] and perhaps directly on the sweat glands themselves.[51]

Not enough is known of the pathogenesis of impotence to state whether it is neurogenic in origin, or secondary to the postural shifts of blood volume. Erection is in part a function of the parasympathetic pelvic nerve, but a disturbance of erection was noted in more than half of the patients subjected to a thoracolumbar sympathectomy.[52] It is possible that the "borrowing-lending" phenomen (hemometakinesia), as described by DeBakey, Burch, Ray and Ochsner,[53] is one mechanism causing impotence. Shunting of blood away from the penile vessels into the expansile asympathotonic vascular bed of the lower extremities would interfere with erection.

Further localization of the site of the lesion responsible for the syndrome is not possible on the basis of present knowledge. However, it has been shown in experiments on animals that lesions in the hypothalamus more often produce disturbances of one function of the sympathetic system without complete destruction of the others[55, 56] than do lesions elsewhere in the brain. This evidence may justify the suggestion that the site of the pathologic changes which give rise to this syndrome lies within the hypothalamus.

Postmortem examination has been done in only three cases; in one of these [57] the brain was not examined, and in the other two[3, 27] the findings were inconclusive in regard to the primary lesion.

A striking phenomenon observed in patients with orthostatic hypotension is their adaptation to long periods of low blood pressure. They tolerate marked hypotensive blood pressures for as long as ten to fifteen minutes, while most normal persons become immediately uncomfortable at systolic pressures of 90 mm. Hg, and develop syncope at systolic pressures of 70 to 80 mm. Hg.[37]

It is of interest that in virtually all of the patients with idiopathic orthostatic hypotension convulsions have not developed. A likely explanation for this fact is that the cerebral circulation is almost immediately restored as the horizontal position is reached. Evidence for this hypothesis is gained from the observations of Stead and Ebert.[19] After their subject had been in the upright position on a tilt table for a given interval, he exhibited generalized clonic movements of the extremities which immediately stopped when he was returned to the horizontal position. Patterson and Cannon[58] measured cerebral blood flow in a subject with postural hypotension and found a progressive fall in cerebral blood flow until syncope occurred. The plateau values observed in normal subjects was never reached.

Another interesting, unexplained observation is that most of these patients are elderly men who withstand many daily episodes of marked hypotension over a period of years without development of myocardial infarction, and with little electrocardiographic evidence of coronary artery disease. One can only speculate about why such patients, whose ages place them in the population group with the greatest incidence of coronary artery disease, show little evidence of it. There is experimental evidence to suggest that, although in hypotension ab-

solute coronary blood flow is decreased, it is increased relative to the total cardiac output and cardiac work.[59, 60] Coronary flow is relatively increased until a certain low critical level is reached, at which time it is sharply curtailed.[61] It appears then that there is relatively adequate blood supply to the myocardium in this type of hypotension even when syncope occurs.

The lack of electrocardiographic changes in idiopathic orthostatic hypotension is in contrast to the situation which obtains in so-called sympathotonic hypotension,[18] in which electrocardiographic changes are not uncommon.[40, 62, 63]

Summary

1. The concomitant occurrence of anhidrosis and impotence with idiopathic orthostatic hypotension, a triad first described by East and Brigden, is reviewed and emphasized. Two new cases conforming to this clinical syndrome are described.

2. This syndrome is most common in males over 40 years of age in whom postural vertigo, syncope, weakness, anhidrosis and impotence are the most frequent complaints. The major physical signs consist of postural hypotension, slow, relatively constant pulse rate, and dry skin. Most of the patients have a low normal basal metabolic rate and frequently have slight nitrogen retention, but none of the laboratory findings is diagnostic. Although the application of heat results in little or no sweating, parenteral pilocarpine induces generalized diaphoresis.

3. The treatment of patients with this syndrome is unsatisfactory. Neither vasopressor drugs nor measures to increase fluid volume have been generally beneficial although both have been helpful in certain patients.

4. Evidence in the literature as well as that obtained in the two cases added herewith suggests that the pathologic physiology of this syndrome includes lack of arteriolar and venous constriction and absence of reflex tachycardia when patients assume the upright posture. Central nervous system lesions, as yet incompletely defined, but possibly in the hypothalamus, are thought to be responsible for anhidrosis and impotence.

5. It is of interest that patients with this affliction remain remarkably free of the signs and symptoms of coronary artery disease, despite the unfavorable combination of age and prolonged exposure to marked hypotension. A possible explanation for this observation is presented.

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The Effect of Procaine Amide (Pronestyl) in Clinical Auricular Fibrillation and Flutter

By G. MILLER, M.D., S. L. WEINBERG, M.D., AND A. PICK, M.D.

Procaine amide (Pronestyl) was administered to patients with auricular fibrillation and flutter in an attempt to restore sinus rhythm. Thirteen of 20 patients with auricular fibrillation had sinus rhythm re-established. Several of the patients who were not converted with procaine amide were later restored to sinus rhythm with quinidine.

FOR MANY YEARS the restoration of sinus rhythm in patients with auricular fibrillation and auricular flutter has been limited primarily to the use of quinidine and its allies. Other agents have occasionally been used without too satisfactory clinical effects.

In animal experiments, procaine hydrochloride has been shown to exert a markedly depressant action on conduction of the cardiac impulse[1]. Procaine hydrochloride has been employed locally and parenterally in treating cardiac arrhythmias arising during surgical procedures in anesthetized patients and has been tried in various clinical instances of spontaneous cardiac irregularities[2]. While sometimes useful under the former circumstances, its central stimulating effects have precluded its application in the unanesthetized patient.

Recently a procaine derivative, the amide analogue of procaine has been introduced[3]. This agent, procaine amide (Pronestyl), is free of central nervous stimulating effects in the dosages used and is applicable in unanesthetized patients. The experimental data of Newman and Clark[4, 5] demonstrated that procaine amide exerts a slowing effect on conduction and produces a decrease of irritability of auricular muscle of the rabbit and the dog. These observations have led us to explore the sphere of usefulness of the drug in the conversion of auricular fibrillation and flutter to sinus rhythm in clinical instances of these arrhythmias.

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MATERIAL AND METHODS

Our material and the therapy used are listed in table 1. There were 20 patients with auricular fibrillation; of these, 13 had chronic auricular fibrillation. The latter term was arbitrarily applied to those patients who were known to have auricular fibrillation for two weeks or more. Their ages ranged from 37 to 71 years and the duration of the arrhythmia from 16 days to more than three years. Five of these patients had rheumatic heart disease and seven had hypertensive and/or arteriosclerotic heart disease.

Of seven patients with paroxysmal auricular fibrillation, five had hypertensive and/or arteriosclerotic heart disease and one patient (case 2) with no previous evidence of heart disease developed auricular fibrillation one day following an appendectomy.

All three patients with auricular flutter had arteriosclerotic heart disease; in two the auricular flutter was paroxysmal while the duration of the arrhythmia was unknown in the third patient.

Except for five of the patients with paroxysmal auricular fibrillation and one patient with paroxysmal auricular flutter, all were receiving digitalis at the time conversion was attempted. Two of the patients with auricular flutter were partially digitalized. Procaine amide was given orally in the majority of cases, intramuscularly in one case each of paroxysmal and chronic auricular fibrillation, and intravenously in two cases of auricular flutter. Initially there was some variation in the oral doses, but subsequently the following schedule was generally employed: 500 mg. every two hours for five doses on the first day, 750 mg. every two hours for five doses on the second day and similar 250 mg. increments on the following days until toxicity or regular sinus rhythm occurred. The highest single dose was 1500 mg., and the highest dosage in one

TABLE 1.—*Clinical Data on Twenty-three Patients Treated with Procaine Amide**

Case	Age	Sex	Clinical Diagnosis†	Auricular Arrhythmia	Duration	Digitalization	Maximum Procaine Amide Dosage	Toxicity	Rhythm after Therapy†
1	66	M	H.A.S.H.D.	Parox. aur. fib.	4 days	+	On a q. 2 hr. schedule mg.: 500-500-750-1500-1500-1500-1500.	None	SR
2	60	M	A.S.H.D.(?) postop.	Parox. aur. fib.	2 hrs.	−	1000 mg. followed in 1½ hrs. by 750 mg.	None	SR
3	57	F	H.A.S.H.D.	Parox. aur. fib.	2 hrs.	−	One dose 500 mg.	None	SR
4	74	F	A.S.H.D.	Parox. aur. fib.	3 hrs.	−	One dose 1000 mg.	None	SR
5	62	M	A.S.H.D.	Parox. aur. fib.	14 hrs.	−	1:00 p.m. 500 mg; 6:00 p.m. 500 mg.	None	SR
6a	55	M	H.A.S.H.D.	Parox. aur. fib.	10 days	+	1000 mg. followed in 3 hrs. by 500 mg.	None	SR
6b				Recurrence of aur. fib.	4 days	+	1000 mg. q. 3 hrs. × 4	None	SR
7	70	M	A.S.H.D. postop.	Parox. aur. fib.	1 day	−	750 mg. q. 2 hrs. × 3 (I.M.)	None	SR
8	63	M	H.A.S.H.D.	Chronic aur. fib.	2½ yrs.	+	On a 2 hr. schedule mg.: 750-1000-1250-1500-1500-1500-1500-1000.	Yes	Unchanged
9	45	F	R.H.D.	Chronic aur. fib.	2 yrs.+	+	1000 mg. q. 2 hrs. × 5	None	Unchanged
10	51	F	R.H.D.	Chronic aur. fib.	3 yrs.+	+	1000 mg. q. 2 hrs. × 5	Yes	Unchanged
11	78	M	H.A.S.H.D.	Chronic aur. fib.	years	+	500 mg. q. 4 hrs. × 7	None	SR
12	71	M	A.S.H.D.	Chronic aur. fib.	1 yr.+	+	1000 mg. q. 4 hrs. × 5	None	Unchanged
13	59	M	A.S.H.D.	Chronic aur. fib.	16 days+	+	1000 mg. q. 2 hrs. × 4	None	SR
14	50	M	R.H.D.	Chronic aur. fib.	3 mos.+	+	1000 mg. q. 2 hrs. × 3	Yes	Unchanged
15	56	M	A.S.H.D.	Chronic aur. fib.	1½ yrs.	+	1250 mg. q. 2 hrs. × 5	Yes	Unchanged
16	35	F	R.H.D.	Chronic aur. fib.	51 days	+	1000 mg. q. 2 hrs. × 4	Yes	SR
17	51	M	A.S.H.D.	Chronic aur. fib.	‡	+	1250 mg. q. 2 hrs. × 6 followed by 2 doses of 1500 mg. q. 2 hrs.	Yes	SR
18a	58	M	H.A.S.H.D.	Chronic aur. fib.	at least 16 days: probably months	+	1000 mg. q. 2 hrs. × 5	None	SR
18b				Recurrence		+	1000 mg. q. 2 hrs. × 5	None	SR
19	47	M	R.H.D.	Recurrence	1 month+	+	1500 mg. q. 2 hrs. × 6	Nausea	Unchanged

TABLE 1.—*Continued*

Case	Age	Sex	Clinical Diagnosis†	Auricular Arrhythmia	Duration	Digitalization	Maximum Procaine Amide Dosage	Toxicity	Rhythm after Therapy†
20	76	M	A.S.H.D.	Recurrence	Probably months	+	1250 mg. × 1 (I.M.)	None	SR
21	68	M	A.S.H.D.	Parox. aur. flutter	1 day	Partial	550 mg. in 6 min. (I.V.)	None	SR
22	72	M	H.A.S.H.D.	Aur. flutter	Unknown	Partial	500 mg. q. 2 hrs. × 2	None	Unchanged
23	50	M	A.S.H.D. postop.	Parox. aur. flutter	2 hrs.	–	750 mg. in 3½ min. (I.V.)	Transient fall of blood pressure	SR

* All patients, unless otherwise specified, received oral medication.

† A.S.H.D.: Arteriosclerotic Heart Disease
H.A.S.H.D.: Hypertensive Arteriosclerotic Heart Disease
R.H.D.: Rheumatic Heart Disease
SR: Sinus Rhythm

‡ This patient, after at least six months of auricular fibrillation, had been converted to sinus rhythm with quinidine six weeks previously. Omission of maintenance therapy resulted in a recurrence of fibrillation which was present for about two weeks prior to procaine amide therapy.

day was 11.5 Gm. in case 8. Six patients with chronic auricular fibrillation unsuccessfully treated with procaine amide were later treated with quinidine sulfate (table 3). Case 19 was started on quinidine 15 hours after his last dose of procaine amide. In all others who received quinidine, 36 or more hours were allowed to elapse after the last dose of procaine amide before quinidine therapy was started.

RESULTS

All seven patients with eight bouts of paroxysmal auricular fibrillation who received procaine amide were converted to sinus rhythm (tables 1 and 2). The duration of auricular fibrillation prior to therapy ranged from two hours in case 3 to at least 10 days in case 6 (table 1). Cases 3, 4 and 5 returned to sinus rhythm following relatively small doses (500 to 1000 mg.) of the drug and the possibility of spontaneous conversion cannot be excluded. However, larger doses of procaine amide were required for normalization of rhythm in the four other instances. Case 6 was restored to sinus rhythm, but when the maintenance dose of procaine amide was decreased to 500 mg. four times a day auricular fibrillation recurred. Procaine amide was then again used successfully in higher doses to re-establish sinus rhythm. In case 7, sinus rhythm was restored after intramuscular therapy.

Of 13 patients with chronic auricular fibrillation who received procaine amide six returned to sinus rhythm (tables 1 and 2). Except for case 20, there was electrocardiographic evidence of the presence of auricular fibrillation of at least two weeks duration in all patients. The duration of the arrhythmia in case 20 is unknown but it was thought to have been present several months prior to therapy. Of five cases with chronic auricular fibrillation with rheumatic heart disease only one was converted to sinus rhythm with procaine amide although the medication was given in sufficient quantity (table 1) to produce toxic manifestations in three of four failures. In three of the rheumatic patients who were not converted with procaine amide, quinidine sulfate was given later and was successful in restoring sinus rhythm in all (table 3).

Of eight patients in whom chronic auricular fibrillation was associated with arteriosclerotic and/or hypertensive heart disease, sinus rhythm was restored by procaine amide in five. Case 18 was converted a second time when a reduction in his maintenance therapy was followed by a recurrence of auricular fibrillation. All three failures in the hypertensive arteriosclerotic group were subsequently tried briefly on quinidine sulfate (table 3). One patient (case 13) returned to sinus rhythm.

The results of procaine amide treatment in

the cases of auricular flutter, used intravenously in two cases and orally in one, will be mentioned below with the discussion of the electrocardiographic observations.

In one patient (case 1) auricular fibrillation was diagnosed clinically. In all other patients the auricular mechanism was proved by electrocardiogram prior to therapy. Electrocardiographic changes observed under procaine amide medication consisted in alterations of auricular

TABLE 2.—*Summary of Results of Procaine Amide Treatment*

	Patients			Total Trials		
	No.	Converted to Sinus Rhythm	%	No.	Converted to Sinus Rhythm	%
Paroxysmal auricular fibrillation	7	7	100	8	8	100
Chronic auricular fibrillation	13	6	46	14	7	50
Auricular flutter	3	2	67	3	2	67
Total	23	15	65	25	17	68

TABLE 3.—*Patients with Chronic Auricular Fibrillation Who Received Procaine Amide and Quinidine Sulfate on Different Occasions*

Case No.	Procaine Amide			Quinidine		
	Converted to Sinus Rhythm	Maximum Dosage Received	Toxicity	Converted to Sinus Rhythm	Dosage Received	Toxicity
10	No	1000 mg. q. 2 hrs. × 5	Nausea and dizziness	Yes	1st day 0.4 Gm. q. 2 hrs. × 4 2nd day 0.4 Gm. q. 2 hrs. × 7 3rd day 0.6 Gm. q. 2 hrs. × 6	Ringing in ears
12	No	1000 mg. q. 4 hrs. × 5	None	No	1st day 0.2 gm. q. 3 hrs. × 5 2nd day 0.4 Gm. q. 3 hrs. × 5 3rd day 0.6 Gm. q. 3 hrs. × 5 4th day 0.6 Gm. q. 3 hrs. × 5	None
14	No	1000 mg. q. 2 hrs. × 3	Nausea, vomiting and dizziness	Yes	1st day 0.4 Gm. q. 2 hrs. × 5 2nd day 0.6 Gm. q. 2 hrs. × 5 3rd day 0.8 Gm. q. 2 hrs. × 4	Nausea and vomiting
15	No	1250 mg. q. 2 hrs. × 5	Nausea and dizziness	Yes	0.4 Gm. q. 2 hrs. × 5	None
8	No	1500 mg. q. 2 hrs. × 5	Dizziness, blurred vision and visual hallucinations	No	0.4 Gm. q. 2 hrs. × 5	None
19	No	1500 mg. q. 2 hrs. × 6	Nausea	Yes	0.4 Gm. q. 2 hrs. × 5 (started 15 hrs. after last dose of procaine amide)	None
17	Yes	1250 mg. q. 2 hrs. × 6 followed by 2 doses 1500 mg. at 2 hr. intervals	Dizziness, nausea and vomiting	Yes	1st day 0.4 Gm. q. 2 hrs. × 5 2nd day 0.6 Gm. q. 2 hrs. × 5	None

rate and rhythm, of the ventricular rate and of the duration of the Q-T interval and are illustrated in figures 1 to 4. The mechanism of conversion to a regular rhythm was observed in eight cases of chronic auricular fibrillation and in two cases of auricular flutter, but only in a single case of paroxysmal auricular fibrillation who developed sinus rhythm with frequent auricular premature systoles (case 3, fig. 1*b*). In cases of chronic auricular fibrillation procaine amide effected a slowing of the auricular rate five times (fig. 2*d*) and produced a stage of auricular flutter three times (figs. 1*c*, 2*e*). Auricular flutter, both induced and pre-existent, responded to further administration of the drug by slowing of the rate of auricular oscillations before the onset of regular sinus rhythm. Thus it would appear that conversion was prone to occur abruptly in cases with the paroxysmal form of the arrhythmia and more gradually in its chronic manifestation.

In case 23, the auricular arrhythmia was replaced, after a short period of sinus tachycardia, by an ectopic rhythm of nodal origin persisting over several days (fig. 3*e*). Conversion of auricular fibrillation and flutter to nodal rhythm was observed in the present series in two other instances; in case 14 following quinidine and in case 22 (fig. 4*e*) after massive digitalization. In both instances procaine amide in doses insufficient for conversion had produced undesired effects (toxicity in case 14 and excessive acceleration of the ventricular rate in case 22).

An untoward increase of ventricular rate under procaine amide medication was observed in 6 instances. Cases 9, 16 (fig. 1*c*) and 17 (figs. 2*d* and *e*) are examples associated with gradual slowing of the rate of auricular oscillations in the course of conversion of chronic auricular fibrillation into sinus rhythm. In two attempts to convert pre-existent auricular

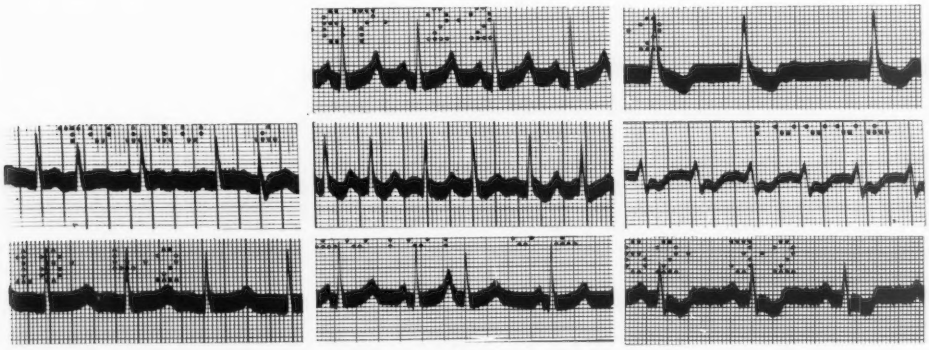

FIG. 1. Effect of pronestyl on auricular rhythm and on Q-T duration. All tracings in lead II.

(*a*) Case 7. *Upper strip:* 8/1/51, five days after esophagectomy. Auricular fibrillation, average ventricular rate 110. Q-T duration not measurable. *Lower strip:* 8/2/51, after a total dose of 2.25 Gm. Pronestyl intramuscularly. Sinus rhythm, rate 80. Note marked prolongation (+0.16 second) of Q-T duration.

(*b*) Case 3. *Upper strip:* 3/8/51. No cardiac therapy. Q-T interval prolonged (+0.06 second). *Middle strip:* 3/19/51. Paroxysm of auricular fibrillation. Average ventricular rate 140. Q-T interval not measurable. *Lower strip:* 3/20/51, after single oral dose of 0.5 Gm. Pronestyl. Sinus rhythm with auricular premature systoles, average rate 72. Q-T duration +0.07 second.

(*c*) Case 16. *Upper strip:* 7/2/51. Auricular fibrillation. Average ventricular rate 65 with corresponding duration of Q-T. QRS duration 0.12 second due to right bundle branch system block. *Middle strip:* 7/5/51, a. m., after 3.0 Gm. Pronestyl. Auricular flutter with regular 2:1 A-V conduction. Auricular rate 250, QRS duration 0.12 second, Q-T duration not measurable. *Lower strip:* Same day, p. m., after total of 7.0 Gm. Pronestyl. Sinus rhythm, rate 68, P-R interval 0.22 second, QRS 0.12 second. Note ST–T contour typical for digitalis, without Q-T prolongation. Compare with lower strip of *a*.

flutter, the ventricular rate became alarmingly high because of transient 1:1 conduction during a stage of slowed auricular flutter (figs. 3 and 4). This marked increase of ventricular rate, which occurred despite preceding digitalization in four cases, may be considered as evidence for the unimpaired A-V conduction during procaine amide therapy.

longed Q-T interval did not seem to correlate with the amount of procaine amide used or with clinical signs of procaine amide toxicity. However, it appeared to be influenced by preceding or concomitant digitalization. This was also suggested by the fact, that most instances with normal Q-T duration under procaine amide effect showed the typical "digitalis con-

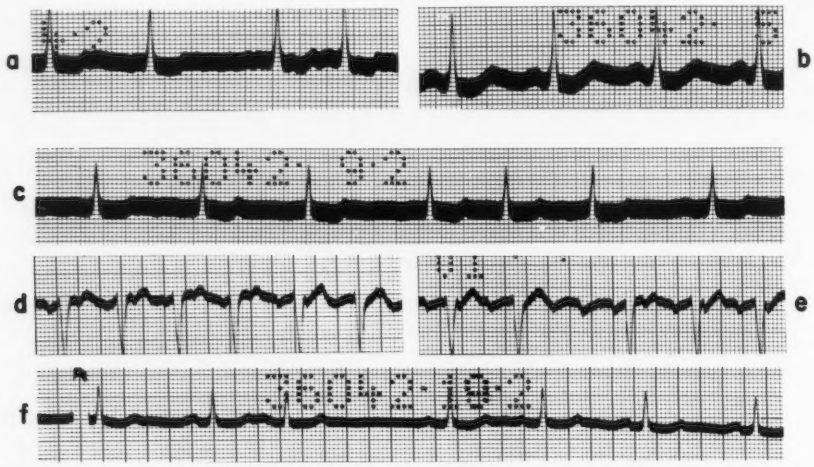

FIG. 2. Comparison of the effect of quinidine (*a* and *b*) and procaine amide (*c* to *f*) on the electrocardiogram. Case 17, on maintenance dose (0.2 mg.) of digitoxin.

(*a*) 1/19/51, lead II: Auricular fibrillation, auricular rate approximately 500, average ventricular rate 66. ST–T configuration typical for digitalis effect. Q-T duration 0.02 second shorter than the expected value.

(*b*) 1/25/51, lead II: After a total dose of 5.0 Gm. of quinidine sulfate in 2 days: Sinus rhythm, rate 75. Note depression of S-T with prolongation of Q-T to +0.09 second.

(*c*) 7/2/51, a. m., lead II: Auricular fibrillation, average ventricular rate 62, Q-T duration +0.02 second.

(*d*) Same day, 9:30 p. m., lead V_1: After total of 7.75 Gm. procaine amide. Impure auricular flutter with irregular A-V conduction. Average auricular rate 250, average ventricular rate 85.

(*e*) Same days as *c* and *d*, 11:30 p. m., lead V_1: After another 1.0 Gm. of procaine amide. Pure auricular flutter with irregular A-V conduction. Auricular rate 206, average ventricular rate 95.

(*f*) 7/3/51, lead II: After total dose of 19.25 Gm. Pronestyl. Sinus rhythm with auricular premature systoles, average rate 58. P-R interval 0.22 second. Note S-T depression and Q-T prolongation (+0.06 second). Compare with *b*.

The Q-T duration before and after medication was evaluated by the method of Hegglin and Holzmann,[6] according to which Q-T intervals exceeding the calculated value for the respective heart rate by ±0.04 second are considered abnormal. Prolonged Q-T duration (greater than +0.04 second) was found in eight instances of the procaine amide experiments, a normal Q-T duration (±0.04 second) in 14 instances. The presence or absence of a protour" of ST-T (fig. 1*c*) while a "pure" procaine amide effect on Q–T could be seen in some undigitalized cases (fig. 1*a*). In one instance (fig. 1*b*) a pre-existent abnormal Q-T showed no further prolongation after a small dose of procaine amide.

Toxicity of Procaine Amide. Contrary to its effect after intravenous administration we encountered no significant hypotensive action of orally administered procaine amide. The toxic

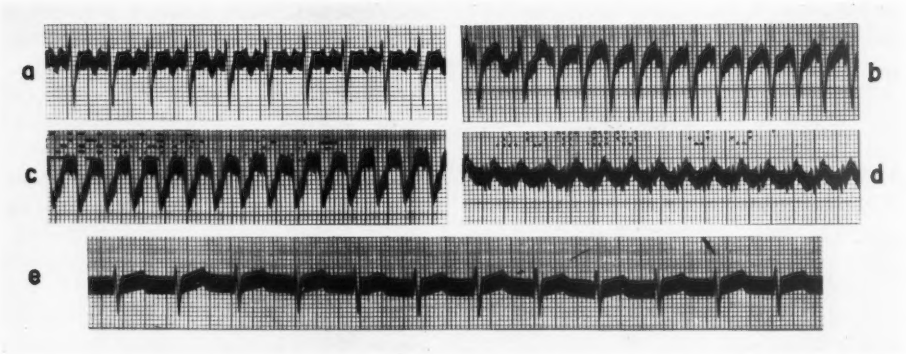

FIG. 3. Conversion of paroxysmal auricular flutter to nodal tachycardia. Case 23, no digitalis.

(*a*) 1/28/51, lead II: Paroxysm of auricular flutter with regular 2:1 conduction. Auricular rate 334, ventricular rate 167. QRS duration 0.10 second. (*b–d*) were taken at short intervals during and following intravenous injection 0.75 Gm. of Pronestyl in three and one-half minutes.

(*b*) Lead II: Average ventricular rate 230, QRS duration 0.10 second. Auricular flutter as underlying rhythm can be recognized at the beginning of the strip, where the ventricular rate is slower and irregular due to transitory change of 1:1 to 3:2 A-V conduction. The auricular rate at these times has slowed down to 276.

(*c* and *d*) Lead II and III: Auricular flutter with regular 1:1 conduction rate 250. QRS duration 0.16 second. Distinct F waves seen in lead III (right strip). Note similarity to ventricular tachycardia.

(*e*) Lead II, taken 30 minutes after *d*. No further therapy. Nodal tachycardia, rate 107. QRS duration 0.06 second.

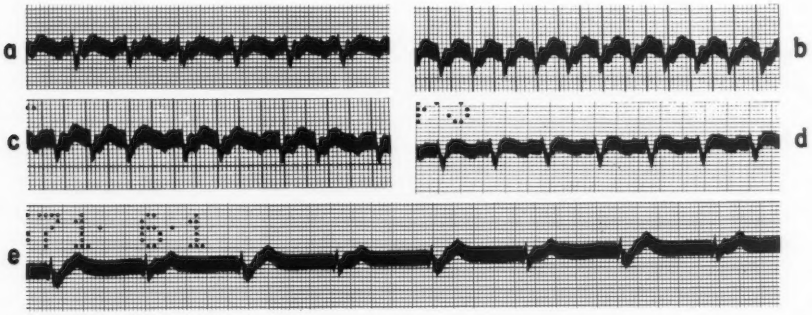

FIG. 4. Effect of oral procaine amide on auricular flutter. Case 22. On 0.1 mg. digitoxin daily.

(*a*) 4/28/51, a. m., lead III: Auricular flutter with regular 2:1 A-V conduction. Auricular rate 250. QRS duration 0.11 second. Incomplete right bundle branch system block.

(*b*) Same day, p. m., lead II: After 1.0 Gm. procaine amide. Auricular flutter with 1:1 conduction. Auricular and ventricular rate 218. QRS duration unchanged. Note similarity to ventricular tachycardia.

(*c*) Shortly after *b*, lead II: Auricular flutter with irregular A-V conduction varying between ratios of 4:3 to 3:2. Auricular rate 210, average ventricular rate 148. QRS duration unchanged.

(*d*) 5/2/51, lead III: Return to a regular 2:1 A-V conduction with auricular flutter persisting, Auricular rate 260.

(*e*) 5/4/51, lead I: Heavily digitalized. Auricular standstill (due to complete S-A block) and nodal rhythm, rate 65. Electrical alternans due to intermittent complete (QRS 0.18 second), superimposed on a persistent incomplete (QRS 0.11), right bundle branch system block.

manifestations encountered were dizziness, nausea, vomiting, and in one case visual hallucinations. Although in some instances (cases 8 and 19) the amount of procaine amide given

was unusually high and was extended to the point of clinical intolerance, in none was ectopic impulse formation or impairment of intraventricular conduction observed which could be ascribed to the action of the drug. In two instances (cases 16 and 22, figs. 1c and 4) a right sided conduction defect present before medication was started, showed no further impairment. The QRS prolongation seen in case 23 (fig. 3) at the peak of the procaine amide effect, disappeared immediately with conversion to nodal rhythm and may, therefore, be ascribed to the excessively high ventricular rate during auricular flutter.

Comment

After screening numerous compounds for possible use in the therapy of cardiac arrhythmia, Mark and co-workers carried out extensive studies with procaine amide.[3–7] While these authors advocated its use in arrhythmias of ventricular origin, Newman and Clark subsequently demonstrated that the drug also had a very definite effect on the conduction and irritability of the auricle of the rabbit and dog.[4, 5] Studies with intravenous procaine amide demonstrated a very definite slowing of the fibrillatory rate of the human auricle.[3, 7, 8] The drug has been successfully used by others[7, 9] in cases of paroxysmal auricular fibrillation. The uniformly good success in restoring sinus rhythm in our seven patients with recent onset of auricular fibrillation is in keeping with these findings. However, six of the 13 patients with chronic auricular fibrillation were also restored to sinus rhythm. This result is somewhat better than anticipated since a number of observers[5, 7, 8-13] have reported the absence of conversions in patients with chronic auricular fibrillation given intravenous procaine amide. It is quite likely that the greater success in more recent investigations using oral procaine amide[14, 15] and in the present study was a result of the higher dosage schedules employed. Reflecting the latter, four of the six patients with chronic auricular fibrillation who were converted had toxic symptoms just prior to, or at the time of, restoration of regular sinus rhythm. Since procaine amide produces its peak blood level approximately one to two hours after each oral dose[3], we feel that a two hour schedule is to be preferred in attempting conversion. To simplify the observation of all patients receiving procaine amide, we generally omitted night time medication and recommended therapy the following morning at the next higher dose schedule. Procaine amide was not only effectively used orally and intravenously but in two patients, who could not take oral medication, the drug was successfully employed by intramuscular administration.

Although weight for weight quinidine is more potent than procaine amide,[14, 16] this fact in itself does not indicate that it is superior in treating auricular flutter and fibrillation. One must have some idea of the toxic to therapeutic ratio before selecting the desired preparation. Some of our data bears on this point and is shown in table 3. Four patients who failed to convert with procaine amide in spite of the fact that the drug was given to toxicity, subsequently were successfully converted with quinidine. Two of the four patients were converted, without any evidence of quinidine toxicity, while the other two had minor symptoms of quinidine intolerance at the time of conversion. A fifth patient (case 17) who was converted to sinus rhythm with quinidine without toxicity, had a recurrence of auricular fibrillation six weeks later after he failed to take maintenance therapy. He was then successfully treated with procaine amide but had toxic symptoms at the time of conversion. From this preliminary experience it would appear that quinidine can restore sinus rhythm in patients with chronic auricular fibrillation more easily and with fewer toxic manifestations than procaine amide.

Kalmansohn and Sampson have stated[17] that the only serious toxic manifestations of quinidine therapy are ectopic ventricular arrhythmias or marked hypotensive effects. Similar toxic signs, including impairment of A-V and intraventricular conduction, have been said to occur with procaine amide.[3, 7, 10, 11, 12, 13, 14, 18] Although clinical intolerance was reached in several of our cases receiving procaine amide, electrocardiographic signs of toxicity were not observed in the present series. The transient widening of QRS in case 23 is explained by aberration of intraventricular conduction with

the rapid heart rate, due to shortening of diastolic recovery time of the conduction system. It has been pointed out[19] that electrocardiographic patterns like those shown in figures 3*c–d* and 4*b* may be mistaken for ventricular tachycardia of ectopic origin and thus may lead to serious therapeutic consequences.

The electrocardiographic alterations found during our procaine amide studies are in accord with previous investigations as far as changes of the auricular mechanism,[14] the auricular and/or ventricular rate[3, 7, 8, 14] and the effect on Q-T duration[3, 7] are concerned. The same discordant effect on auricular and ventricular action (slowing of the former and acceleration of the latter) was seen under procaine amide as was described years ago by Rothberger[20] and Lewis[21, 22] in their studies on the effect of quinine and quinidine on auricular flutter and fibrillation. This includes the deleterious increase of ventricular rate by production of full A-V conduction as seen in two of our cases with auricular flutter. Prolongation of the Q-T interval was seen in about one third of cases treated orally by procaine amide. The shortening effect on the "electrical systole" of digitalis may explain the lack of appearance of Q-T prolongation in the greater part of our material consisting primarily of cases with chronic auricular fibrillation.

The increase in the ventricular rate may be marked in patients with auricular fibrillation and particularly auricular flutter who receive procaine amide, especially if no digitalis has been given. In view of the danger of prolonged, rapid ventricular rates, particularly in the presence of associated heart disease, it is best to give adequate digitalis therapy prior to an attempt at conversion.

The exact mechanism of the action of procaine amide on the auricular and ventricular myocardium is still obscure and requires further experimental clarification. The striking similarity between quinidine and procaine[2] and its amide in their clinical action and effects upon the electrocardiogram invites speculation upon a possible similar mode of action. Prolongation of the refractory period of the isolated rabbit auricle by procaine amide has been demonstrated,[4] and a similar effect on the ventricular myocardium is suggested by the prolongation of the Q-T interval following clinical application of procaine amide. However, the appearance of persistent nodal rhythm after interruption of experimentally produced auricular fibrillation, as previously reported,[23] as well as its appearance in one of our cases cannot be explained by such a mechanism alone. It is possible that, for unknown reasons, secondary mechanisms may become prevalent in certain instances, like stimulation of subsidiary automatic center and/or a depressing action on impulse transmission in the auricles.* The latter mechanism has been especially stressed in recent studies[24] on the action of quinidine in auricular arrhythmias. The similarity to quinidine is further supported by observations of unusually high rates of A-V conduction (276 in case 23), which were ascribed in the case of quinidine to its paralyzing effect upon the vagi.[21]

Summary and Conclusions

1. Twenty cases of auricular fibrillation and three cases of auricular flutter were treated with procaine amide (Pronestyl) in an attempt to restore sinus rhythm.

2. The attempt proved successful in all instances of paroxysmal auricular fibrillation, in 6 of 13 cases with chronic auricular fibrillation and in two of three cases of auricular flutter. The dosage used ranged from a single dose of 500 mg. in a case of paroxysmal auricular fibrillation to 11.5 Gm. in a day given to a patient with chronic auricular fibrillation.

3. In no instance were there electrocardiographic manifestations of toxicity in the present series. In two instances slowing of the rate of auricular flutter by procaine amide with transient 1:1 A-V conduction and aberrant intraventricular conduction imitated the electrocardiographic pattern of ventricular tachycardia of ectopic origin.

4. A striking similarity between procaine amide and quinidine was found in their clinical action as well as in their effect upon the electro-

* Such a complex mechanism was apparently under action and effected by massive digitalization in case 22, figure 4*e*, and produced complete S–A block, nodal rhythm and electrical alternation.

cardiogram. Although this suggests very strongly a similar mode of action of both drugs, further experimental proof is needed.

ACKNOWLEDGMENTS

We are indebted to the attending physicians of Michael Reese Hospital for permission to make these observations on their patients. We are also indebted to Dr. L. N. Katz for his valuable suggestions.

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Neurohemodynamics of Pulmonary Edema

II. The Role of Sympathetic Pathways in the Elevation of Pulmonary and Systemic Vascular Pressures following the Intracisternal Injection of Fibrin

By STANLEY J. SARNOFF, M.D., AND L. CHARLOTTE SARNOFF

The authors criticize the concept of "neurogenic pulmonary edema" as resulting from an increase in pulmonary capillary permeability mediated by nerve impulses to those vessels. They show that one of the methods used to produce "neurogenic pulmonary edema" markedly elevates systemic and pulmonary vascular pressures, the latter to levels high enough to produce pulmonary edema. Vagotomy and/or upper thoracic sympathectomy do not prevent the elevation of pulmonary vascular pressures. Blockade of the sympathetic innervation to the systemic vascular bed lowers the systemic vascular pressures and brings the pulmonary vascular pressures back to normal. The control of pulmonary vascular pressures by sympathetic impulses to the systemic vascular bed is demonstrated.

THE CONCEPT of neurogenic pulmonary edema, which relates central nervous injury, irritation, or stimulation to the pulmonary edema state, has suffered somewhat from a lack of observation of those phenomena concurrently going on in the cardiovascular system.

As a result the view has become widespread that the pulmonary edema state results from an increase in pulmonary capillary permeability mediated by nerve impulses, independent of that hemodynamic change which might readily be expected to produce pulmonary edema, namely, an increase in pulmonary capillary pressure.

One notable exception to the foregoing has been the recent study of Campbell, Haddy, Adams and Visscher,[1] in which these authors demonstrated that increased intracranial pressure produced acute pulmonary edema which was preceded by a rise in both pulmonary arterial and venous pressures. This was not, however, accompanied by arterial hypertension, but instead by bradycardia and a lowered cardiac output. The pathway was demonstrated to be vagal.

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In 1949, Cameron and De,[2, 3] in attempting to produce chronic hydrocephalus in the rabbit, injected a combination of thrombin and fibrinogen into the cisterna magna of the rabbit. The rabbit promptly developed massive, overwhelming, lethal pulmonary edema. The authors felt that this occurred as a result of increased pulmonary capillary permeability resulting from nerve impulses, primarily vagal.

These phenomena seemed worthy of closer hemodynamic scrutiny, especially with regard to those pressure changes occurring in the pulmonary vascular bed. Accordingly, the following study was undertaken.

The integration of this work with other pulmonary edema research by previous investigators will not be done here but will be attempted in a subsequent communication.

METHOD

Eighteen rabbits weighing from 1.6 to 2.9 Kg. were used, and the anesthetic was a 25 per cent solution of urethane given intravenously in doses of 4 cc. per Kilogram. Ninety mongrel dogs weighing from 10.5 to 20.5 Kg. were anesthetized with morphine sulfate 4 mg. per Kilogram, chloralose 48 mg. per Kilogram, and urethane 480 mg. per Kilogram. The morphine sulfate was given intramuscularly 30 minutes prior to the intravenous administration of the latter two agents, which were then given slowly as a mixed warm solution. The results of experiments on these dogs will form the basis of a

subsequent report[4] as well as this one. Sixty-five of these experiments were technically satisfactory from the point of view of yielding significant data.

All pressures studied were obtained by means of the electromanometer[5] and recorded with direct-writing galvanometers which register in rectilinear coordinates. The point of zero reference for pressure determinations was arbitrarily selected as a point 4 cm. above the lowest point on the concave dog board. This, of course, introduced some error in terms of absolute values, since dog size and position varied somewhat from experiment to experiment. This error, however, remained constant throughout any given experiment. Mean pressures were obtained by electrical integration of the full pulse pressures.

In the dog, central systemic venous pressure, pulmonary artery pressure, pulmonary "capillary" pressure,[6] left auricular or pulmonary venous pressure, and femoral arterial or aortic pressure were obtained through appropriately placed catheters, utilizing fluoroscopy when needed. Systemic arterial and left auricular or pulmonary venous pressures were recorded in every dog studied. The pericardium was opened for cannulation of the left auricle but was intact if the pulmonary vein was cannulated instead. Other pressures were recorded as indicated below. Carotid artery and left auricular pressures were measured in four of the rabbits studied.

Two types of dog preparations were used, closed and open chest. When the closed chest preparation was used, left auricular pressures were obtained through a catheter passed retrograde up the femoral artery and aorta and through the aortic and mitral valves.[6, 7] With the open chest preparation direct cannulation of either the left auricular appendage or a lobular pulmonary vein was used. In some experiments pulmonary artery and pulmonary "capillary" pressures were obtained by means of a twin lumen catheter, one lumen of which opened 6 cm. proximal to the distal lumen orifice. Final positioning of the catheters was checked by fluoroscopy when indicated and by analysis of the pulse contours obtained. All experiments were done with a tracheotomy tube in place, and respiration was maintained by a modified Starling pump in both the open and closed chest experiments. Heparin in the catheters was employed to avoid clotting.

When autonomic blockade was desired, 0.04 to 0.05 mg. per Kilogram of *d*-3,4-(1′,3′-dibenzyl-2′-ketoimidazolido)-1,2-trimethylene thiophanium *d*-camphor sulfonate (Ro 2-2222) were given intravenously.* This agent has been shown by Randall and co-workers[8] to block sympathetic ganglions and prevent stimulation of the vagus.

* Supplies of this compound were made available through the generosity of Dr. Elmer L. Sevringhaus of Hoffmann-La Roche, Inc., Nutley, N. J. This agent has been given the name Arfonad.

Spinal anesthesia was administered through previously placed subarachnoid catheter according to the method of Co Tui.[9] When total spinal anesthesia was desired, 5 cc. of a 4 per cent solution of procaine hydrochloride were rapidly injected.

In rabbits the atlanto-occipital membrane was visualized and 0.2 to 0.3 cc. thrombin and 1.0 to 2.0 cc. fibrinogen were injected through a needle in rapid succession. One rabbit received only the fibrinogen. In the early dog experiments a similar technic was employed, using 3.0 cc. thrombin and 10 to 13 cc. fibrinogen. The solutions were made up by dissolving 0.12 Gm. thrombin (500 units) in 5 cc. isotonic saline and by dissolving 0.4 Gm. fibrinogen in 15 cc. isotonic saline. The combined injection will hereinafter be referred to as fibrin. In later dog experiments the atlanto-occipital membrane was opened widely (1.5 cm.) and the solutions simply sprayed over the dorsal aspect of the medulla with a catheter pointing towards the tentorium. This permitted ready egress of fluid and prevented a rise in cerebrospinal fluid pressure.

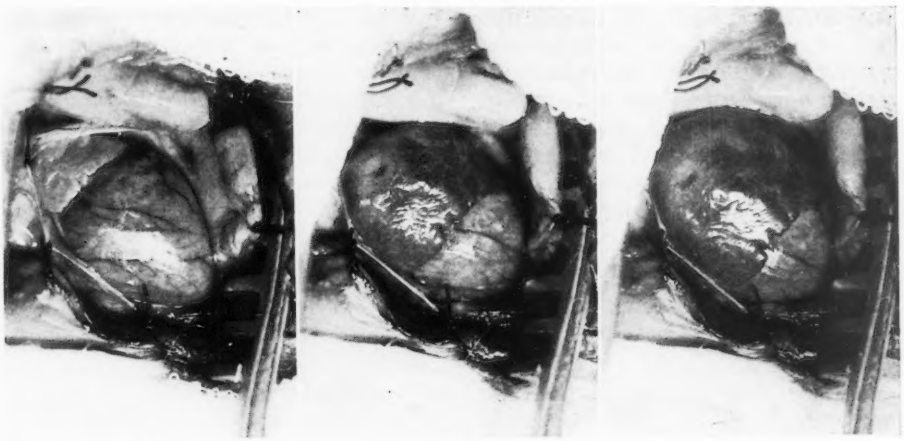
When the preparatory maneuvers had been completed, a positive displacement pump was used to accomplish the intravenous infusion of 10 cc. per Kilogram of isotonic saline in one minute. Either one, two, or occasionally three such "standard" infusions were given in the 30-minute period prior to the injection of fibrin. Prior to the intracisternal injection of fibrin, these infusions were never observed to elevate pulmonary venous pressure more than 2 mm. Hg. For purposes of comparison, in some experiments this "standard" infusion was given one or more times after the intracisternal injection and again after ganglionic blockade.

Results

Observations in the Rabbit

1. *Response of the Rabbit to the Intracisternal Injection of Fibrin.* The response of the rabbit to the intracisternal injection of fibrin was as previously described.[2, 3] A generalized rigor, usually opisthotonos, defecation and urination, and a variable respiratory pattern ranging from apnea to intense tachypnea and hyperpnea occurred. When apnea occurred, positive pressure breathing was applied until the death of the rabbit. Frequently, pink froth and fluid poured out of the tracheal cannula or, in those instances where positive pressure breathing was used, through the escape hole in the tracheal cannula just prior to or following death. The latter occurred in from 2.5 to 35 minutes following the intracisternal injection. The lungs of the rabbits at postmortem examination were

as described by Cameron and De[2, 3] and as previously shown.[10] Pulmonary edema, varying in intensity from moderate to severe, occurred in all but one of the rabbits. A systematic hemodynamic study was not made in the rabbit, but several findings were of interest. When a left thoracotomy incision and opening of the pericardium was performed, it was possible to visualize the left auricle and its response to the intracisternal injection of fibrin. Figure 1 shows photographs taken just before and 70 and 105 seconds after the fibrin injection. It can be seen that significant enlargement of the left auricle occurred. The left ventricle also appeared to enlarge in this and other experiments, but was not as readily photographed. One rabbit receiving an intracisternal injection of fibrinogen alone without preliminary thrombin also developed acute pulmonary edema which was as pronounced and more rapidly lethal (2.5 minutes) than the average rabbit receiving both agents.



A *B* *C*

FIG. 1. Rabbit heart seen through left thoracotomy incision and incised pericardium. Rabbit is on its right side with head to the left in each picture. *A*. 10 seconds prior to injection. Left auricle is in systole. *B*. 70 seconds after intracisternal injection of 0.3 cc. thrombin and 3.0 cc. fibrinogen in rapid succession. Note enlargement of left auricle. *C*. 105 seconds after injection. Auricle almost covers the ventricles. Auricular pulsations were hardly visible in the grossly distended left auricle shown in *C*.

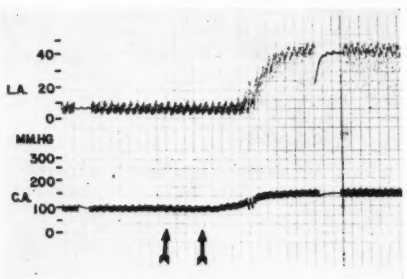


FIG. 2. Pressure tracings from left auricle and right carotid artery of rabbit. Pressure in millimeters of mercury at the left. Solid lines are electrically integrated (mean) pressures; others are full pressures in this and subsequent illustrations. 1 mm. (each fine vertical line) = 1 second. Intracisternal injection of 0.3 cc. thrombin at first arrow and 3.0 cc. of fibrinogen at second arrow.

2. *Response of Left Auricular and Carotid Arterial Pressures.* Following the intracisternal injection of fibrin, a rise in carotid arterial and left auricular pressure developed in the four rabbits in which these pressures were measured (fig. 2).

Observations in the Dog

Characteristically, following the intracisternal injection of fibrin, there was a sharp elevation of arterial pressure and, more or less simultaneously, a rise in pulmonary artery,

"capillary," and venous pressures. This was accompanied by a transient motor and respiratory response similar to, but less marked than, that seen in the rabbit. Central systemic venous pressure rose either slightly (3 mm. Hg) or markedly (30 mm. Hg). When an elevation of pulmonary vascular pressures did occur, it usually reached a peak sometime within the first minute and then either remained elevated, fell slightly to a sustained plateau, or returned to control levels in about five minutes. In the latter case, they could be readily re-elevated by the administration of one "standard" infusion.

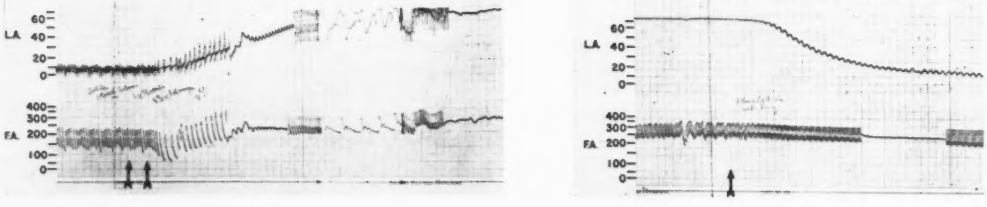


FIG. 3. Pressure tracings from vena cava, pulmonary artery, left auricle and femoral artery of dog. A fibrin injection 11 minutes previously had been only partially successful in producing hypertension. Solid lines = electrically integrated (mean) pressures; other lines, full pulse pressures. Chart speed is 2.5 mm. per second except for brief portion in *A* where speed is 25 mm. per second. *A*. Intracisternal injection of 3 cc. thrombin at first arrow and 11 cc. fibrinogen at second arrow. *B*. Starts four minutes after end of *A*. 0.04 mg. per kilogram Ro 2-2222 given intravenously at arrow. Note return of vena cava, pulmonary artery, and pulmonary venous pressures to normal levels with only slight fall of femoral arterial pressure.

The cardiovascular response of the dogs was more or less consistent, but not infrequently deviations occurred from the pattern described above. In one dog a bradycardia without hypertension developed. This was in one of the earlier experiments in which the atlanto-occipital membrane had not been opened and the vagi were intact. In one-fourth of the dogs a striking systemic arterial hypertension developed, but left auricular pressure rose only slightly or not at all. In general, the noncharacteristic type of response occurred less frequently as: (a) more experience with the injection technic was obtained, and (b) the open atlanto-occipital membrane technic described above was used, and (c) two or occasionally three "standard" infusions rather than one were given prior to intracisternal fibrin injection.

1. *The Development of Acute Pulmonary Edema in the Dog after the Intracisternal Fibrin Injection.* Since the study was concerned with hemodynamic observations and the effect of systemic vasodilation on pulmonary vascular pressure, only two dogs which developed elevated left auricle pressures after the fibrin were left untreated. These showed generalized pulmonary edema at postmortem examination.

2. *Effect of Intracisternal Fibrin on the Arterial and Venous Pressures of the Pulmonary and Systemic Vascular Beds.* Figure 3*A* shows the hypertension that developed in vena cava, pulmonary artery, left auricle, and femoral artery following the intracisternal injection of fibrin. The initial period of bradycardia was replaced by tachycardia. It was assumed that pulmonary capillary pressure would be slightly higher than left auricular pressure, or, in this

instance, more than 70 mm. Hg. It is noteworthy that the mean pressure gradient between femoral artery and thoracic vena cava was markedly widened, whereas the pressure gradient between pulmonary artery and vein was hardly altered following the fibrin injection. The highest left auricular pressure obtained after the fibrin injection is shown in figure 3. In those dogs in which a significant pulmonary vascular hypertension developed, the post-fibrin increment of pulmonary venous pressure varied between 10 and 64 mm. Hg.

3. *Effect of the Autonomic Blocking Agent, Ro 2-2222, on Elevated Pulmonary and Systemic Vascular Pressures.* Since the pathways were suspected of being autonomic, an autonomic blocking agent was used to ascertain whether the elevated pulmonary vascular pressures could be lowered by ganglionic blockade. Figure 3*B* is a record from the same experiment as shown in Figure 3*A* and starts four minutes after the end of that tracing. Vena cava, pulmonary artery, and pulmonary venous pressures promptly fell to control levels after the intravenous injection of 0.05 mg. per kilogram of Ro 2-2222. It is important to note that the return to normal levels of central venous and pulmonary vascular pressures occurred simultaneously with a relatively slight fall in systemic arterial pressure. In all instances where elevated pulmonary arterial and venous pressures developed after the intracisternal injection of fibrin, the administration of Ro 2-2222 was followed by a fall of these pressures to control levels or below.

4. *Effect of Vagotomy on Elevated Left Auricular Pressure.* It was important to find out if the causal pathway was vagal (fig. 4). Following the intracisternal fibrin injection and the development of arterial hypertension and tachycardia, left auricular pressure rose from a control level of 11 mm. Hg to 51 mm. Hg. This then gradually fell to the sustained plateau of 30 mm. Hg as seen at the beginning of the tracing in figure 4. Bilateral cervical vagotomy was followed by a further slight elevation of left auricular pressure. Partial ganglionic blockade with Ro 2-2222 then produced a slight fall of arterial pressure and a prompt return of left auricular pressure to the control level. Bilateral cervical vagotomy was performed either prior to or during the elvation of pulmonary venous pressure resulting from the intracisternal injection of fibrin in 20 dogs. Prior vagotomy did not protect against the elevation of pulmonary venous pressure. Vagotomy performed during the period of elevated pulmonary venous pressure either did not change this value or, as happened more frequently, caused a further elevation.

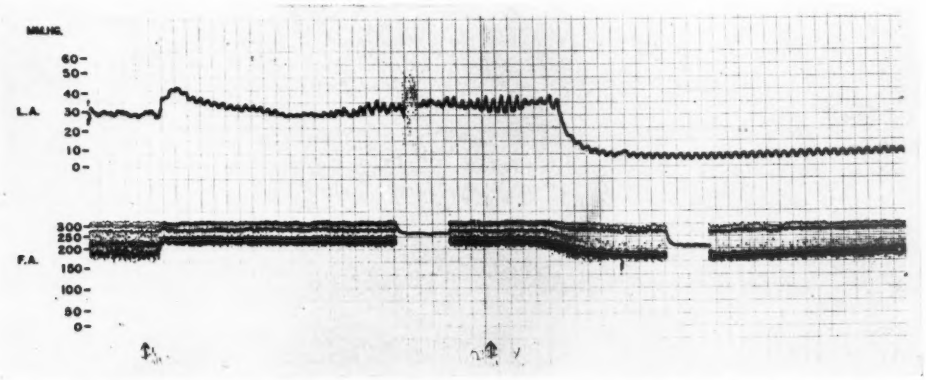


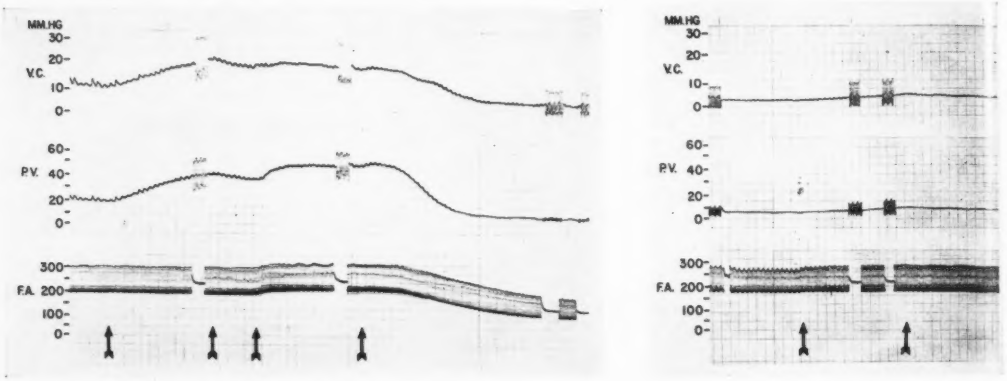
FIG. 4. Pressure tracings from left auricle and femoral artery of dog. Chart speed = 1 mm. per second. 3 cc. thrombin and 11 cc. fibrinogen given into cisterna magna previously (see text). Vagus nerves cut at first arrow. 0.04 per kilogram Ro 2-2222 given intravenously at second arrow.

5. *Effect of Preliminary Bilateral Removal of the Sympathetic Chain from the Stellate to the Fifth Thoracic Ganglion.* The possible role of sympathetic impulses directly to the lung itself

was investigated by making the fibrin injection in dogs from which the sympathetic chains from the stellate through the fifth thoracic ganglions on both sides had been removed intact. This type of experiment was carried out in four dogs, and elevations of pulmonary vascular pressures were obtained in all of them, although the average rise was about one-third less than in those with intact sympathetic ganglions.

6. *Effect of Bilateral Upper Thoracic Sympathectomy and Midcervical and Upper Thoracic Vagotomy and Bilateral Phrenicectomy.* Professor I. de Burgh Daly was kind enough to consider this material. He suggested that the above combination of denervation procedures would strengthen somewhat the position in regard to complete pulmonary denervation and his suggested type of denervation was done in one dog. The intracisternal injection of fibrin was followed in one minute by a rise of vena cava pressure from 4 to 9 mm. Hg, of pulmonary artery pressure from 18 to 38 mm. Hg, of pulmonary "capillary" pressure from 9 to 31 mm. Hg, and of femoral artery pressure from 145/95 to 295/180 mm. Hg.

7. *Effect of "Standard" Infusion on Pulmonary Venous Pressure before and after Intracisternal Fibrin and after Partial Ganglionic Blockade.* It was thought worthwhile to ascertain the effect of a "standard" infusion on pulmonary venous pressure before, during, and after the induction of peripheral vasoconstriction in a dog from which the pulmonary sympathetics had been removed. Figure 5 shows the record of dog 38, in which a bilateral upper thoracic sympathectomy had been performed as described above. Prior to the injection of fibrin, a standard intravenous infusion (10 cc. normal saline per kilogram in one minute) had little effect on pulmonary venous pressure, that is, a rise of 1 mm. Hg. After the fibrin injection pulmonary venous pressure was 21 mm. Hg (start of fig. 5*A*). At that time a "standard" infusion caused a marked rise in pulmonary venous pressure, that is, from 20 to 42 mm. Hg (between first and second arrows). At the third arrow a bilateral cervical vagotomy was done and was followed promptly by a further significant rise of pulmonary venous pressure. Partial blockade of the remaining intact ganglions (those which supply the splanchnic bed



A *B*

FIG. 5. Pressure tracings from vena cava, pulmonary vein, and femoral artery of dog from which the sympathetic ganglions had been removed on both sides from the stellate through the fifth ganglion. Chart speed = 1 mm. per second. Prior to the intracisternal injection of thrombin and fibrinogen a "standard" saline infusion elevated pulmonary venous pressure 1 mm. Hg. The injection of thrombin and fibrinogen elevated pulmonary venous pressure from 5 to 21 mm. Hg as seen at the beginning of *A*. A "standard" saline infusion was administered between the first and second arrows in *A*. The vagus nerves were cut at the third arrow and at the fourth arrow 0.05 mg. per kilogram Ro 2-2222 was given intravenously. *B* starts 14 minutes after end of *A*. A "standard" saline infusion was given between the first and second arrows.

and vascular areas from D-6 and below) was followed by a prompt fall to normal levels of the elevated pulmonary venous pressure. Fourteen minutes later (fig. 5*B*) while the dog was still partially under the influence of the ganglionic blockade, the effect on pulmonary venous pressure of another "standard" infusion was similar to that obtained prior to intracisternal fibrin, namely, a negligible rise. The same result with Ro 2-2222. It was, however, more gradual in onset. This time factor was presumably related to the slower development of the subarachnoid chemical sympathectomy.

9. *Effect of Curare Administered Prior to the Intracisternal Fibrin.* Because it was thought that the diffuse motor activity that follows the intracisternal injection of fibrin might play a role in this phenomenon, curarization with de-

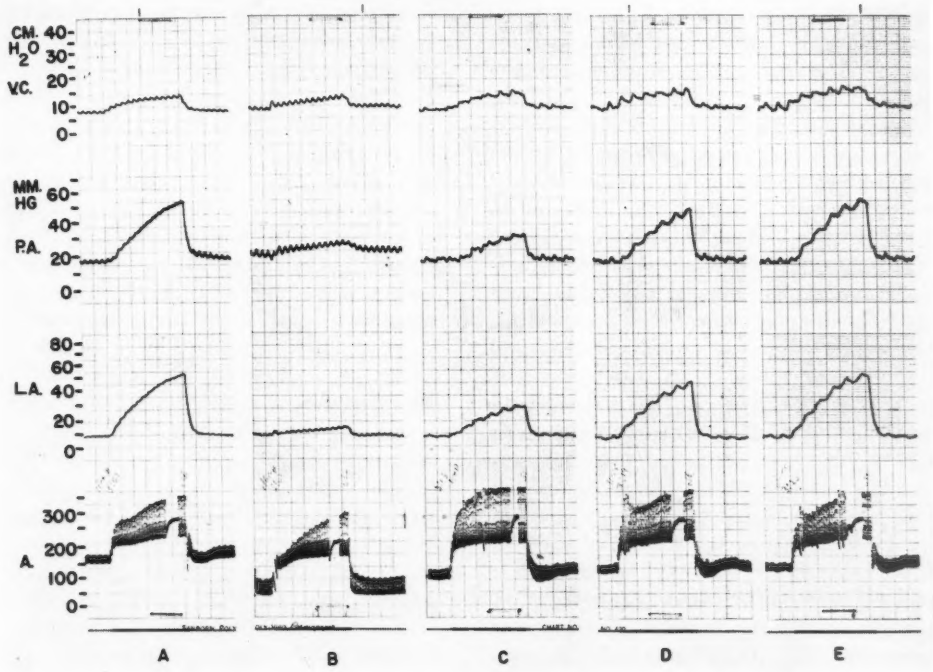


FIG. 6. Pressure tracings from vena cava, pulmonary artery, left auricle and root of aorta in dog. Chart speed = 1 mm. per second. Signal at the bottom. Vagus nerves cut. Aortic occlusion at the beginning of each signal and release at the end. *A*, *B*, *C*, *D*, and *E* are six minutes apart. Two minutes after each aortic occlusion, 0.5 per cent of dog's weight of isotonic saline given. Ro 2-2222, 0.05 mg. per kilogram, given intravenously two minuts prior to *B*.

with regard to the effects of a "standard" infusion were obtained in dogs from which the pulmonary sympathetics had not been removed.

8. *Effect of Spinal Anesthesia after the Intracisternal Injection of Fibrin.* In three dogs the subarachnoid injection of procaine hydrochloride during the phase of elevated pulmonary venous pressure was followed by a fall in this value comparable in extent to that obtained camethonium was carried out to the point of apnea in order to prevent muscular contractions. The subsequent fibrin injection was, of course, not accompanied by a motor response, but vena cava pressure rose from 5 to 9 mm. Hg; pulmonary artery pressure from 15 to 36 mm. Hg; pulmonary "capillary" pressure from 8 to 32 mm. Hg; and femoral arterial pressure from 140/60 (m = 90) to 300/220 (m = 250) mm. Hg. In another type experiment curariza-

tion with decamethonium did not lower previously elevated pulmonary vascular pressures.

10. *Effect of Total Aortic Occlusion on Pulmonary Vascular Pressures before and during Ganglionic Blockade.* Another type of experiment, in addition to those cited above, was performed with the hope of throwing some light on the role of changes in peripheral vascular blood volume as well as changes in peripheral vascular resistance when peripheral vasoconstriction occurs. After bilateral vagotomy, the left subclavian artery was tied off at its point of emergence from the aorta. Subsequently, the simultaneous clamping of the arch of the aorta and the brachycephalic artery for precisely 30 seconds stopped the output of the left ventricle except for the blood going through the coronary arteries. The carotid sinuses were subjected to lowered pressure during the aortic occlusion. The elevation of pressure in vena cava, pulmonary artery, left auricle, and aorta were found to be more or less constant if the aortic occlusion was done at six-minute intervals and if 0.5 per cent of the dog's body weight of isotonic saline was injected in the second minute after each aortic occlusion. Figure 6 shows the results of this type of experiment. Before ganglionic blockade when the aortic occlusion produced peripheral vasoconstriction because of the lowered carotid sinus pressure, pulmonary vascular pressures rose sharply (fig. 6*A*). After ganglionic blockade the same aortic occlusion produced less of a rise in pulmonary vascular pressures (fig. 6*B*). As the ganglionic blockade wore off, the response approximated its previous magnitude (figs. 6*C*, *D*, and *E*).

Discussion

None of the above data exclude the possibility that nerve impulses may influence pulmonary capillary permeability. However, it is clear from the experiments we have described that there is an alternative explanation to that put forth by Cameron and De.[2, 3] That is to say, the activity of nerve impulses consequent upon the intracisternal injection of fibrin in some way brings about an elevation of pulmonary capillary pressure of such an extent as to be reasonably expected to account for the edema that occurs.

Just what occurs locally when the medulla is bathed in fibrin is not readily apparent. There is evidence to support the view that this is a nonspecific irritative or locally stimulating phenomenon, since Jarisch and associates[11] reported that veratrine introduced into the cisterna magna of rabbits also produced pulmonary edema. This was confirmed by Horst and coworkers.[12]

In other experiments not described above intracisternal protoveratrine was also followed by marked elevations of pulmonary vascular pressures but not as immediate in onset. Further evidence that the clotting process is not essential to this phenomenon is also indicated by the rapidity with which the changes develop and, also, by the observation that fibrinogen alone produced acute pulmonary edema in the one rabbit to which it was given.

In view of the striking changes in heart rate and systemic and pulmonary arterial and venous pressures, it seems that some pronounced stimulation, either direct or indirect, is being brought to bear upon the cardiovascular regulatory centers of the brain. This is about as far as our understanding of this part of the sequence goes.

Since bilateral cervical vaogtomy neither prevents the rise in pulmonary vascular pressures nor lowers elevated pressures when done after the fibrin injection, vagal impulses do not appear to play a causative role in the production of these elevated pressures in the dog. In the majority of instances when vagotomy was performed after the elevation of pulmonary vascular pressures, it was followed by a further rise indicating that vagal activity was, if anything, conferring a partial protective effect.

It is well to emphasize the basic difference between the experimental syndrome described above and that used by Campbell, Haddy, Adams and Visscher.[1] These authors observed that increasing intracranial pressure by the inflation of a subdural balloon over the dog's cerebrum was followed by a moderate elevation of pulmonary arterial and venous pressures and eventually pulmonary edema. However, systemic arterial pressure either fell or remained at control levels and the pulse rate was slowed. Vagal blockade with atropine returned pul-

monary vascular pressures to normal, elevated cardiac output, and averted the development of pulmonary edema. There is a reasonably satisfying comparison to be made between the experimental syndrome produced by these authors and that which is seen clinically in the postoperative neurosurgical patient or one with brain injury from other causes.

The experimental pulmonary edema syndrome, which has been the subject of this communication, more closely resembles the cardiovascular type of pulmonary edema, since it is accompanied by hypertension, tachycardia, and markedly elevated pulmonary arterial and venous pressures. As will also be seen from a subsequent communication,[4] cardiac output is restricted in relation to the rise in left auricle pressure. It may be argued that the hypertension seen in these experiments is more severe than that seen clinically and that the conditions are "unphysiologic." It should be remembered, however, that the experimental syndrome described in the above experiments is one in which an attempt was made to produce a cardiovascular type of pulmonary edema in an organism with a normal heart. Clinical pulmonary edema of the cardiovascular type generally occurs in an organism in which disease has significantly diminished the work capacity of the heart as a pump. The diseased human heart may reasonably be expected to fail at a lower challenge threshold than that of the normal dog.

The elevation of pulmonary vascular pressures apparently does not depend upon the integrity of the sympathetic nerve supply to the lung, since these pressures rose with intracisternal fibrin even after a bilateral upper thoracic sympathectomy had been performed. The combined denervation procedure suggested by Prof. I. de Burgh Daly likewise did not prevent the elevation of pulmonary vascular pressures following intracisternal fibrin. The average elevation of pulmonary venous pressure was less than that seen in dogs with intact sympathetic ganglions. It must be remembered, however, that the sympathectomy performed also deprived a significant portion of the peripheral vascular bed of the possibility of participating in the constrictor response.

From flow data to be presented elsewhere,[4] it will be clear, as might be anticipated, that the elevation of systemic arterial pressure is largely the result of increased peripheral vascular resistance. Further evidence that centrally mediated nerve impulses to the lung are not an important factor in the rise of pulmonary vascular pressures will be found in the fact that the pulmonary vascular resistance is not elevated following the intracisternal fibrin. In any case, it would be difficult to hold pulmonary vasoconstriction responsible for the marked elevations of left auricular pressure observed above.

The administration of a "standard" infusion uniformly produced a significant rise in pulmonary venous pressure after peripheral vasoconstriction had been induced by intracisternal fibrin. Contrariwise, the same infusion had little or no effect on pulmonary vascular pressures if it was administered either prior to the intracisternal fibrin or after pulmonary vascular pressures had been returned to normal by means of ganglionic blockade.

Of considerable interest in the interpretation of the above data is the fact that pulmonary vascular pressures may be elevated by impulses travelling over sympathetic fibers to the peripheral vascular bed, and conversely, they may be returned to normal by sympathetic blockade of the peripheral vascular bed. This relationship may help to reconcile in some measure the opposing views of those who do and those who do not believe that there is significant nervous control of the volume and pressure of the blood in the pulmonary vascular bed.

It was clear from gross observation of the left auricle (fig. 1) and pulmonary veins as well as consideration of the pressure elevations in the pulmonary vascular bed that a marked increase in the volume of blood between the pulmonic and mitral valves takes place after medullary stimulation with fibrin. That there is a striking increase in peripheral vascular resistance and apparent left ventricular failure will be shown in a subsequent publication.[4] However, to consider this the complete explanation of the observed phenomena would be an oversimplification of the problem, for generalized peripheral vasoconstriction, in addition to

increasing peripheral vascular resistance, also decreases the volume of blood which can be held in the peripheral vascular bed. This extra volume of blood must then be shifted to some other area, presumably to a vascular bed with little or no constrictor potential, the lung.

As seen in figure 6*A* when the aorta was occluded for 30 seconds, left auricular pressure rose sharply. During the period of aortic occlusion it is to be expected that the low pressure in the carotid sinuses induced peripheral vasoconstriction. In figure 6*B*, two minutes after ganglionic blockade, aortic occlusion resulted in a much smaller elevation of left auricular pressure. As the ganglionic blockade wore off, the rise in left auricular pressure gradually regained its previous level (fig. 6*C*, *D*, and *E*). Leaving aside the effect of Ro 2-2222 on the coronary vessels, it is reasonable to assume that the aortic occlusion produced a similar impedance effect whenever it was applied. With constrictor impulses to the peripheral vascular bed intact, left auricular pressure rose sharply, and when these were blocked, the rise was much less pronounced. It would seem that peripheral vasoconstriction should be thought of as producing a blood shift from periphery to lung as well as increasing the resistance against which the left ventricle works, insofar as the effect on pulmonary capillary pressure is concerned. This has recently been confirmed in other studies utilizing a technic for the continuous registration of changes in pulmonary blood volume.[13]

The therapeutic implications of the principle of peripheral vasodilation in the management of acute pulmonary edema are apparent, especially in view of previous data from patients in acute pulmonary edema who were treated with spinal anesthesia.[14] That a significant lowering of pulmonary venous pressure can be achieved with only a slight lowering of arterial pressure gives rise to the hope that this principle may prove useful in the treatment of the pulmonary edema accompanying coronary insufficiency as well as that accompanying hypertension. Moreover, closer scrutiny of the above figures reveals that left auricular or pulmonary venous pressure began to fall at a time when systemic arterial pressure had fallen hardly at all. Theoretically, at least, if it is possible to adjust the degree of peripheral vasodilation delicately, it should be possible to diminish significantly elevated pulmonary venous pressures with only a slight fall in arterial pressure. Preliminary clinical results with Ro 2-2222 suggest that delicate adjustment of peripheral vascular resistance is possible.[15]

The authors are keenly aware of the pitfalls to be encountered in the casual application of Starling's law to the patient or intact animal with acute heart failure. And yet, even taking into account the fact that there may be a whole "family" of curves instead of a single curve to express the relationship between end diastolic pressure and stroke work, it seems reasonable to conclude that in at least some of the experiments shown above, the left ventricle was working at a more advantageous point on the Starling curve after peripheral vasodilation had produced a lowering of left auricular pressure.

Horst and co-workers[12] using intracisternal veratrine found that the development of pulmonary edema in the rabbit was prevented by the prior administration of the hydrogenated derivatives of ergotamine. Cruchaud and Vermeil[16] using intracisternal fibrin in rabbits found that the pulmonary edema was prevented by Dibenamine in three rabbits and by dihydroergotamine in five. Neither group measured left auricular or pulmonary venous pressures but their data suggested that the sympathoadrenal system was in some way involved.

In experiments not described above Ro 2-2222 did not prevent the pressor response to epinephrine and also did not lower arterial pressure which was previously elevated by epinephrine. This makes it unlikely that endogenously secreted epinephrine was a decisive factor either in the elevation of pulmonary vascular pressures or in their return to normal with ganglionic blockade. It does not, however, preclude the possibility that endogenously secreted epinephrine may have contributed to the over-all response.

Lastly, the authors are obliged to justify the use of a new term in connection with acute pulmonary edema. The term "neurogenic pulmonary edema" has been used by many authors to convey a variety of meanings. In the minds

of some it represents an influence on pulmonary capillary permeability in the absence of an increase in pulmonary capillary pressure. In the view of others it represents any pulmonary edema in which nerve impulses have a primary causal role without special consideration of whether or not they cause a significant elevation of pulmonary capillary pressure. In recent years the authors have come to feel that its usefulness as a means of explicit communication is far outweighed by the confusion it engenders. It was thought that a more causally specific term would be helpful. The phrase "neurohemodynamic pulmonary edema" has been found useful in our laboratory and is herewith defined.

Neurohemodynamic pulmonary edema is that state wherein an increase in the rate of transfer of fluid from pulmonary capillary to the extravascular space of the lung is brought about by an increase in pulmonary capillary pressure, which in turn is brought about either directly or indirectly by nerve impulses.

Summary and Conclusions

1. The intracisternal injection of thrombin and fibrinogen (fibrin) is followed by stimulation of the cardiovascular centers. This produces an elevation of pulmonary and systemic arterial and venous pressures in the dog and carotid and left auricular pressures in the rabbit. It also produces a grossly observable increase in the blood volume of the left auricle and pulmonary veins.

2. Bilateral vagotomy prior to the fibrin injection does not prevent this elevation, nor does intercurrent vagotomy lower the elevated pulmonary vascular pressures in the dog.

3. Bilateral upper thoracic sympathectomy (stellate to fifth thoracic ganglion) performed prior to the fibrin injection does not prevent the elevation of pulmonary vascular pressures, nor does total pulmonary denervation.

4. Elevated pulmonary vascular pressures return to normal promptly after ganglionic blockade with Ro 2-2222.

5. It is felt that nerve impulses causing *peripheral* vasoconstriction can create a substantial increase in the volume and pressure of blood in the pulmonary vascular bed. Conversely, effective blockade of these impulses can reverse these phenomena.

6. It is noteworthy that only a small decrease in peripheral arterial pressure may be required to return markedly elevated pulmonary vascular pressures to normal.

7. On a theoretic basis peripheral vasodilation, by lowering left auricular pressure from markedly elevated levels, alters hemodynamics in such a way that the left ventricle works at a more advantageous point on Starling's curve.

8. The intravenous infusion of 10 cc. of isotonic saline per kilogram in one minute has little effect on pulmonary venous pressure (<2 mm. Hg) in the normal anesthetized dog. In the presence of marked peripheral vasoconstriction, however, a similar infusion produces striking elevations of pulmonary venous pressure.

9. The shift of blood from periphery to lung is probably not only a matter of left ventricular failure but also dependent in part upon the fact that a vascular bed of high constrictor potential (systemic) can shift blood into an area of low constrictor potential (pulmonary) and thereby elevate the pressure in the latter. Conversely, peripheral vasodilation can shift blood from lung to periphery.

10. The use of the term "neurogenic pulmonary edema" has, in the authors' opinion, ceased to be a useful means of explicit communication. The suggestion is made that it be discarded in favor of what, under appropriate circumstances, is felt to be a more meaningful term, namely, "neurohemodynamic pulmonary edema." A definition of this term has been suggested.

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Graded Reduction of Arterial Pressure in Man by Means of a Thiophanium Derivative (Ro 2-2222)

Preliminary Observations on Its Effect in Acute Pulmonary Edema

By STANLEY J. SARNOFF, M.D., WALTER T. GOODALE, M.D., AND L. CHARLOTTE SARNOFF

The authors describe the use of a ganglionic blocking agent which acts almost entirely as a peripheral vasodilator with minimal side effects in man. This substance acts almost instantaneously when given intravenously, with the depressor effect quantitatively controlled by regulating the infusion rate without tachyphylaxis over several hours. Depressor effect of the drug disappears 2 to 15 minutes after stopping the infusion and is blocked promptly by intravenous ephedrine, neosynephrine or norepinephrine. The authors discuss its use in the treatment and elucidation of the basic mechanisms of acute pulmonary edema.

RANDALL, Peterson, and Lehmann have described a ganglionic blocking agent which reduces arterial pressure in anesthetized dogs and cats.[1] This compound, *d*-3,4-(1′,3′-dibenzyl-2′-ketoimidazolido)-1,2-trimethylene thiophanium *d*-camphor sulfonate, will be called by its code number, Ro 2-2222,* for convenience. It effectively lowers arterial blood pressure at much lower dosage levels than tetraethylammonium chloride.[1] Furthermore, during recent investigations[2–5] on the role of the autonomic nervous system in experimentally induced pulmonary edema, Ro 2-2222 has been found to lower pulmonary venous pressure to normal from previously induced levels of 20 to 70 mm. Hg. These favorable experimental data have prompted us to investigate and report the action of Ro 2-2222 in man.

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METHOD

Administration. After preliminary investigation, Ro 2-2222 was given intravenously 27 times to 13 hypertensive patients and twice to two normotensive patients in one of two ways: (a) as single or multiple injections of either 0.1 or 0.2 mg. per kilogram of body weight, given in 30 seconds intravenously; or (b) as a continuous intravenous drip of 1 or 2 mg. of the drug per cc. in a 5 per cent dextrose solution.

After an intravenous infusion of 5 per cent dextrose had been established, control observations were made and the infusion of Ro 2-2222 in 5 per cent dextrose was started by turning a three-way stopcock in the line in such a manner that the patient was probably unaware of the change. This continuous infusion method was thought by the authors to yield the most significant information. Table 1 lists the patients.

Arterial pressure was recorded by means of the sphygmomanometer adhering to the criteria of Ragan and Bordley.[6] In one patient brachial and pulmonary arterial pressures were recorded directly by means of the electromanometer.[7] The heart rate was counted with the aid of a stopwatch. All patients were studied in the horizontal position with one pillow under the head except (a) the pulmonary edema patients described below, and (b) one patient with hypertensive encephalopathy, to whom Ro 2-2222 was given while in the lateral decubitus position in order to obtain readings of cerebrospinal fluid pressure.

Skin temperatures were taken either by means of the Rauh apparatus or the continuously recording, multiple lead, Brown potentiometer as used in previous studies.[8]

When the continuous drip method was employed, the dripper was calibrated in terms of drops per cubic centimeter so that conversion to milligrams per minute could be made. The data obtained will be presented in that form. The cold pressor test was performed by immersing one hand up to the wrist in ice water for two minutes.

Observations

Single or Multiple Intravenous Injections of Ro 2-2222. The effects of single or multiple intravenous injections are shown in figure 1. Figure 1*A* shows the brevity of the depressor response when 0.2 mg. per kilogram was used.

Table 1.—*Clinical Findings in Thirteen Hypertensive and Two Normotensive Patients*

	Name	Age	Admission Blood Pressure	Maximum Urine S. G.	Blood Urea Nitrogen	Cardiomegaly	Cardiac Failure	Encephalopathy
1.	I. N.	68	240/140	1.019	14	+	○	+
2.	V. H.	34	220/140	1.010	18	+	○	○
3.	H. H.	26	220/155	1.018	20	+	○	○
4.	A. M.	50	250/170	1.014	85	+	+	+
5.	H. G.	50	225/135	1.019	12	+	○	○
6.	W. S.	41	190/130	1.009	85	+	+	○
7.	M.D.	45	230/120	1.024	12	+	○	○
8.	E. M.	42	250/160	1.020	21	+	○	○
9.	F. G.	40	220/125	1.010	13	+	+	+
10.	F. M.*	42	130/90	1.024	10	○	○	+*
11.	J. H.	44	184/110	1.012	27	+	○	○
12.	W. M.	39	290/178	1.015	37	+	○	○
13.†	E. G.	32	220/140	1.010	25	+	+*	○
14.†	A. L.	14	170/120	1.012	203	+	+*	+
15.†	G. H.	45	70/50–90/60	1.017	47	+	+*	○

* Normotensive patient with central nervous system syphilis.

† Patients with acute pulmonary edema.

Figure 1*B* indicates the reproducibility of the depressor response when a second dose was given 22 minutes after the first. Figures 1*C* and 1*D* suggest that a reasonable type of dose-response relationship exists insofar as can be determined from the depressor effects of 0.1 and 0.2 mg. per kilogram. Figure 1*C* further shows the similarity of the depressor response to a dose of 0.2 mg. per kilogram given to the same patient on two successive days.

In figure 1*E* is shown the effect of a single dose of 0.2 mg. per kilogram on cerebrospinal fluid pressure in a patient with hypertensive encephalopathy. About 12 cc. of spinal fluid had been removed just prior to the period during which the observations were made, and the cerebrospinal fluid pressure was returning to its previous level when the intravenous injection of Ro 2-2222 was made. A temporary and slight reduction in cerebrospinal fluid pressure occurred. Unfortunately, no data were obtained during the more prolonged depressor effect obtained with the continuous drip technic as described below. (See addendum.)

As seen in figure 2*A*, tachyphylaxis did not occur when a total of 1 mg. per kilogram was administered in divided doses over a period of 31 minutes. This figure confirms the nature of the dose-response relationship as seen above, since 0.1 mg. per kilogram given at the beginning and end of the sequence had less of an effect than doses of 0.2 mg. per kilogram administered in the interim. The over-all effect was an irregular lowering of arterial pressure. However, the reproducibility of the response was demonstrated.

Ro 2-2222 Administered as a Continuous Intravenous Drip. In figure 2*B* the effect on arterial pressure of a continuous infusion of 3 mg. per minute can be seen. The cold pressor test, which yielded a substantial rise of both systolic and diastolic pressures during the control period, did not produce a pressor response during the administration of Ro 2-2222. Cessation of the infusion was followed by a prompt return of arterial pressure to control levels.

Figure 3 shows the effect on arterial pressure of varying the rate of infusion. Note that different degrees of reduction in arterial pressure could be obtained and that this depended upon the rate of administration of the drug. In addition, changes in arterial pressure levels occurred promptly so that the new level was apparent within a few minutes after changing the rate of administration. The induced fall of arterial pressure could be made either abrupt or gradual and to those levels found desirable to meet the therapeutic or experimental requisites.

The response of skin temperature during the administration of Ro 2-2222 is shown in figure 3*B*, wherein it can be seen that the cutaneous temperatures of the right and left great toe

rose during the hypotensive periods and fell when arterial pressure rose toward control levels. The injection of 50 mg. of ephedrine sulfate intramuscularly elevated arterial pressure and lowered skin temperature while the administration of Ro 2-2222 was being continued.

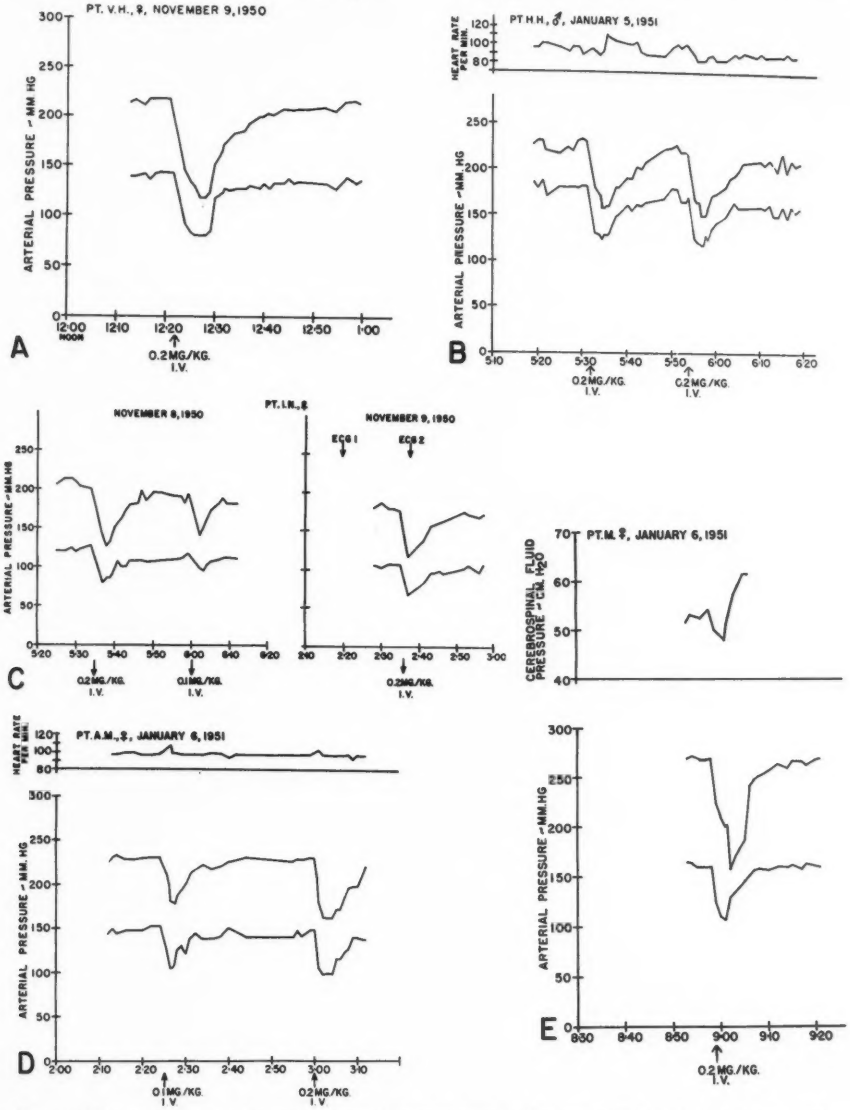

FIG. 1. The effects of single and repeated intravenous injections of Ro 2-2222 in hypertensive patients. See text.

In figure 3*C*, data from a normotensive patient, the administration of 50 mg. ephedrine sulfate intravenously produced a marked elevation of arterial pressure from the hypotensive level produced by Ro 2-2222. In this patient, as in the patient of figure 2*B*, the cold pressor test failed to elevate arterial pressure during the administration of the drug.

The response of the pulse rate seen in figure

2*B* was the greatest change observed. In one other instance it rose 15 beats per minute but returned to control levels during the continued administration of the drug. In other patients the pulse rate changed less than 10 beats per minute and most frequently decreased.

In one patient (previous data shown in fig. 3*B*), Ro 2-2222 was given as a continuous infusion while the patient was on the artificial kidney. Figure 4 shows the reduction in pulmonary arterial pressure that accompanied the reduction in systemic arterial pressure 3.5 minutes after the start of the infusion of Ro 2-2222 at the rate of 3.7 mg. per minute.

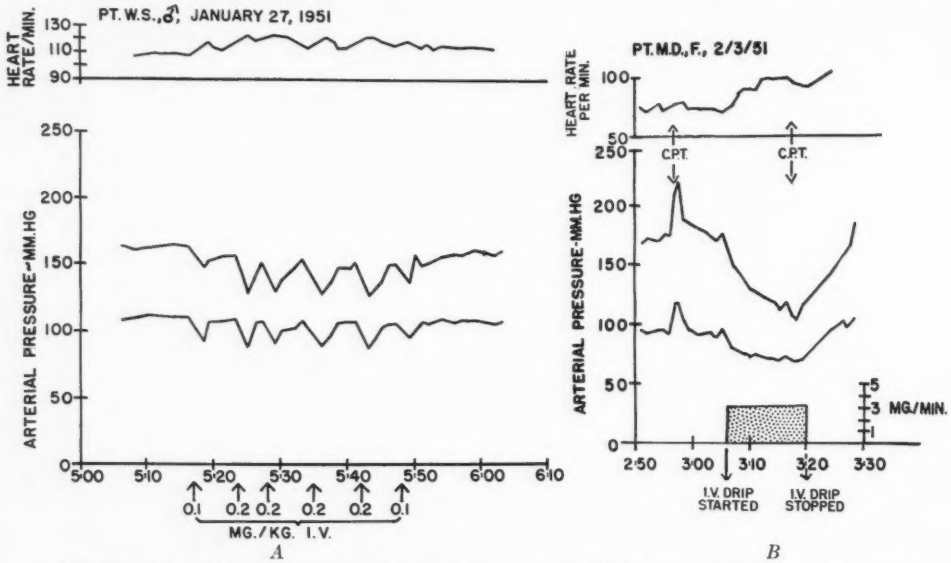

FIG. 2*A*. Effect of repeated single injections. See text. *B*. Effect of continuous intravenous infusion of Ro 2-2222 (2 mg. per cc. in 5 per cent dextrose) at rate of 3 mg. per minute. C. P. T. = cold pressor test.

Acute Toxicity. Insofar as the gross observation of the patient is informative, the acute toxicity of Ro 2-2222 in the doses administered was as follows:

One patient (fig. 1*A*) had restlessness and a temporary clouding of the sensorium during the hypotensive period after the arterial pressure had been abruptly lowered. These symptoms also occur with abrupt hypotension induced by other means, such as tetraethylammonium chloride or high spinal anesthesia. They were not seen in those patients in whom the continuous infusion method was used. In two patients with hypertensive encephalopathy, gastrointestinal symptoms were observed when the intravenous drip was increased to the point of tolerance. Nausea, retching, and the passage of flatus occurred in one, and nausea and vomiting in the other. Although both patients had been nauseated and had vomited several times previously on the same day, the reaction, coming as it did at the time of the highest dose level, was attributed to the drug. This occurred, however, at a dosage level several times higher than was required for an effective depressor response. In two other patients, the hypotensive phase during the administration of Ro 2-2222 was accompanied by persistent yawning, frequent eructation, and the passage of flatus. Yawning accompanied the continuous administration of Ro 2-2222 in all the hypertensive patients to whom it was given in effective depressor doses, except in the patients with acute pulmonary edema described below. It did not occur in the one normotensive patient studied.

When the agent was administered for any length of time, dryness of the mouth always

occurred. This can reasonably be attributed to the parasympatholytic activity of the drug as described by Randall and co-workers.[1] No other side reactions were observed.

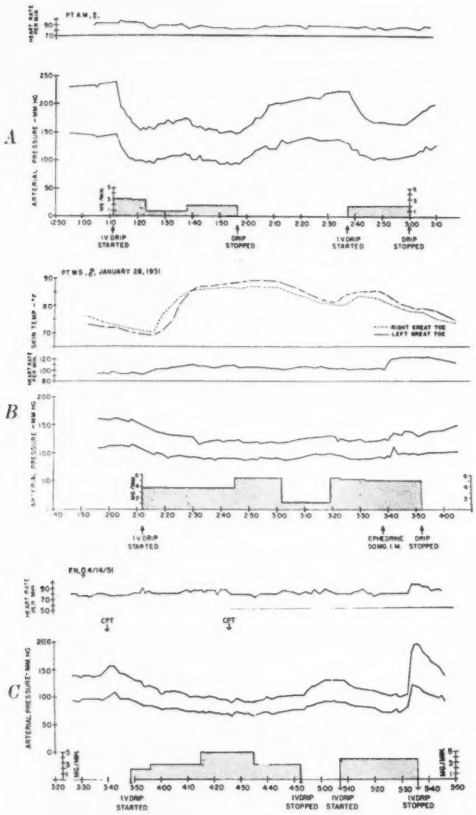

FIG. 3*A–C*. Effect of varying the rate of administration of Ro 2-2222. Drug given as a solution containing 2 mg. per cc. in 5 per cent dextrose. Changes in skin temperature shown in *B*. Note effect of 50 mg. ephedrine sulfate intramuscularly in *B* and ephedrine sulfate, 50 mg., intravenously in *C*. This latter was given at 5:33 p.m. C.P.T. = cold pressor test.

CASE REPORTS

Case 1. Treatment of Acute Pulmonary Edema Associated with Hypertension

E. G. (No. 8B756) was a 32 year old single man with hypertension for 10 years, admitted because of paroxysmal dyspnea and mild edema. He was a well developed, well nourished man, often sweating and apprehensive. Blood pressure was 220/140 with a definite pulsus alternans; pulse, 88; respirations, 20. The fundi showed fresh and old hemorrhages and exudates, marked narrowing of the arterioles and arteriovenous nicking, and grade I papilledema. The chest was clear to percussion and auscultation. The heart was enlarged with a heaving apex impulse, normal sinus rhythm, and a diastolic gallop at the apex.

Laboratory Data. The urine concentration was 1.025 with pH 5.5, 1 to 3 plus protein, occasional red cells, white cells, granular casts, and no growth on culture. Hematocrit was 45. Blood urea nitrogen values were 18 and 30 mg. per 100 cc. Vital capacity was 3900 cc. Urea clearance was 49 cc. per minute, maximum. Intravenous pyelograms were normal.

X-ray films and fluoroscopy of the lungs showed clear lung fields. The heart was 27 per cent enlarged with predominance of the left ventricular segment.

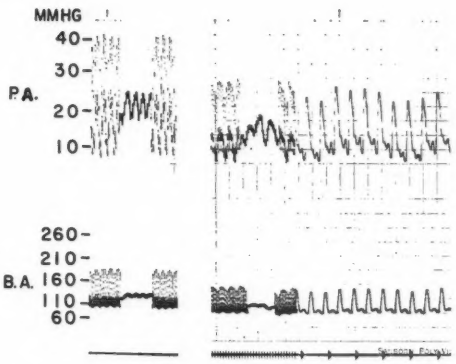

FIG. 4. Upper tracing = pulmonary artery. Lower tracing = brachial artery. Slow speed = 1 mm. per second. Fast speed = 10 mm. per second. Solid black line represents electrically integrated (mean) pressures; other represents full pulse pressures. Tracings at right obtained 3.5 minutes after starting infusion of Ro 2-2222 at rate of 3.7 mg. per minute. Same patient as 3*B* on a different occasion.

On the thirteenth hospital day, following a period of obvious emotional stress, the patient developed extreme apprehension, orthopnea, and rales throughout both lungs up to level of the clavicle. Pulse rate rose to 156, respirations to 44, blood pressure to 280/160. He was unable to lie flat for even a few moments. There was a marked pulsus alternans. A polyvinyl tube was then inserted into the right basilic vein approximately 22 inches so as to pass into the superior vena cava. Ro 2-2222 was given at a rate of approximately 1 mg. per minute by continuous intravenous drip. Within 10 minutes, and coincident with a moderate fall in arterial pressure, his respirations slowed and were subjectively and objectively less labored. The pulse rate fell and venous pressure fell from 220 to 90 mm. Pulsus alternans disappeared and most of the rales had

cleared from his lungs. Within 20 minutes he was able to lie flat with comfort and remain so without an elevation of pulse or respiratory rate. At that time there were only a few scattered moist basal rales, and these were gone upon auscultation one hour later. (See figure 5 for details.)

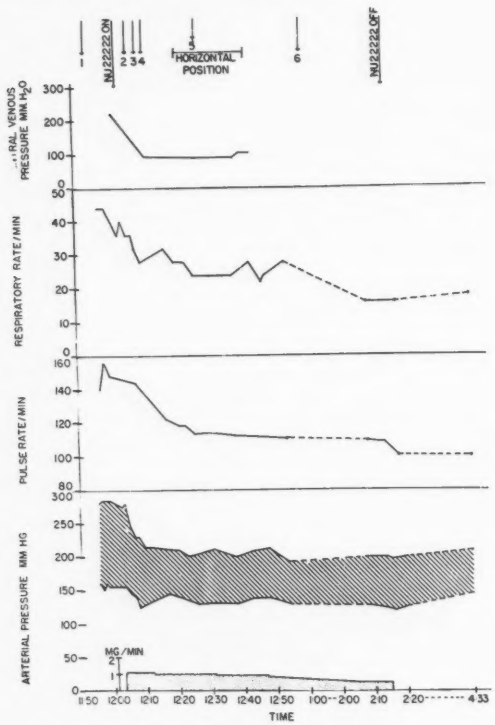

FIG. 5. Data on central venous pressure (corrected), respiratory rate, pulse rate, and arterial pressure from patient in acute pulmonary edema treated with Ro 2-2222. At arrow 1 patient was orthopneic, sweating, markedly apprehensive, had bubbling rales up to the clavicle and was bringing up pink-tinged sputum. At arrow 2 the rales had become distinctly less audible. At arrow 3 the patient volunteered that his breathing felt considerably easier and at arrow 4 was able to tolerate the horizontal position. Auscultation revealed only scattered basal rales, and at arrow 5 he requested lunch. At arrow 6 he ate while the infusion of Ro 2-2222 was still going in. It was discontinued at 2:15 p.m.

After two hours and 12 minutes of intravenous medication, the drip was discontinued and the patient remained comfortable and asymptomatic for the remainder of the day. On the following day, a milder but comparable episode of acute pulmonary edema was promptly relieved following an injection of 0.1 mg. of protoveratrine.

Case 2. Acute Pulmonary Edema Associated with Uremia

A. L. (No. 8B804) was a 14 year old boy, admitted in extremis from renal failure following an attack of acute glomerulonephritis six months previously. His face was puffy, pale, and cyanotic; he was dyspneic and orthopneic, but not edematous. Blood pressure was 170/120; pulse, 104; respirations, 48; rectal temperature, 98.8. The heart was enlarged with regular sinus rhythm and no murmurs, and a rough pericardial friction rub. There were medium and coarse, moist rales throughout both lung fields. The urine showed a specific gravity of 1.012 with 3 plus protein and was loaded with red cells and white cells and occasional hyaline and granular casts. Hematocrit was 20. White blood cell count, 15,600 with 83 per cent polymorphonuclear leukocytes. The blood urea nitrogen was 203 mg. per 100 cc. The carbon dioxide combining power was 16 mM. per liter. Serum sodium was 143 and serum potassium 8.9 mEq. per liter. Electrocardiogram was characteristic of moderate hyperkalemia.

He had already been given 5 mg. of digitoxin and 12 mg. of morphine sulfate. Oxygen therapy had been administered for three hours by means of a face mask. The administration of Ro 2-2222 in doses up to 2.5 mg. per minute failed to induce any objective evidence of improvement or lowering of blood pressure. The same negative result followed 0.12 mg. protoveratrine intravenously. The further administration of morphine sulfate and digitoxin had no significant effect, and the patient died four hours later following a series of convulsions. Autopsy permission was not obtained.

Case 3. Acute Pulmonary Edema Associated with Lower Nephron Nephrosis and Hypervolemia

G. N. (No. 9B198) was a 45 year old housewife who was heavily exposed to a chlorinated hydrocarbon while spraying clothes in a closed room. Over the succeeding five days preceding admission, she became anorexic, developed diarrhea, abdominal cramps, nausea, vomiting, right upper quadrant tenderness, and finally drowsiness, oliguria, and hypotension.

Physical Examination. Her temperature was 102 F.; pulse, 94; respirations, 22; blood pressure, 70/40. She was semistuporous and dehydrated. There were a few moist rales at the right lung base. The heart was normal in size and showed no irregularities or murmurs. The abdomen was moderately distended with gas; peristaltic sounds were reduced but otherwise normal. There was definite tenderness and resistance in the right upper quadrant. There was 1 plus pitting edema of the legs.

Admission Laboratory Data. Findings in urine were: specific gravity, 1.017; pH, 5.0; 3 plus protein; 1 plus sugar; no acetone; 3 or 4 white blood cells, hyaline and granular casts but no red blood cells per

high-power field. Findings in blood were: hematocrit 38 per cent; white blood cell count, 26,500 with 98 per cent polymorphonuclear leukocytes; 16 eosinophils per cu. mm.; urea nitrogen, 47 mg. per 100 cc.; carbon dioxide combining power, 18.6 mM. per liter; serum chloride, 88 mEq. per liter; serum sodium, 120 mEq. per liter; serum potassium, 3.4 mEq. per liter; serum bilirubin, 0.32 mg. per 100 cc.

Hospital Course. She was given 200 cc. of normal saline and 300 cc. of 3 per cent sodium chloride intravenously within the first five hours of admission which, without other medication, was accompanied by a rise in blood pressure to 100/70, a brisk resumption of urine output, and a rise in serum chloride level to 109 mEq. per liter. Hydration was continued over the ensuing 18 hours, but the hematocrit meanwhile fell to 32 per cent, and a slow transfusion was started. After 250 cc. had run in over three hours, the patient developed dyspnea, orthopnea, and both moist rales and asthmatic wheezing throughout both lung fields. The transfusion was discontinued immediately.

Ro 2-2222 was given, 20 mg. intravenously over two minutes. By this time the blood pressure had fallen from 144/92 to 90/66, the respiratory rate from 38 to 28, the venous pressure from 190 to 120 mm. Hg. Within five minutes after starting the drug, the patient noted subjective improvement in her wheezing and was able to tolerate the horizontal position without marked dyspnea. Within 25 minutes after stopping the injection, however, the blood pressure had risen again to 126/88, the respiratory rate to 36, the venous pressure to 155 mm. Hg, and orthopnea and wheezing had returned subjectively to a point comparable to the control period. At 30 minutes, 20 mg. of Ro 2-2222 was given at half the previous rate over four minutes, and the blood pressure fell again, to 90/68, again with relief of wheezing and orthopnea. Eight minutes after stopping this infusion, symptoms had again become severe with a rise of blood pressure to 120/90. This time Ro 2-2222 was given at 4 mg. per minute over 40 minutes with continued relief of orthopnea at a blood pressure level of 100/76. Wheezing virtually disappeared, and there were only scattered bilateral moist basal rales. The patient was then given morphine sulfate, 8 mg. subcutaneously, and Digoxin 1 mg., intravenously with continued relief of the symptoms of acute pulmonary edema.

A laparotomy was performed, under local anesthesia with supplementary doses of morphine, in order to rule out acute cholecystitis as the cause of the severe leukocytosis and right upper quadrant tenderness. An acutely swollen, exquisitely tender liver was found, biopsy of which showed pericholangitis and fatty infiltration consistent with a toxic hepatitis. The gallbladder and pancreas were normal. Diuresis continued over the next few days, with urine outputs of 2,000 to 5,000 cc. daily and gradual return of renal function to normal and without recurrence of acute pulmonary edema.

Discussion

Peripheral vasodilation induced by spinal anesthesia in patients with acute pulmonary edema has been shown previously to be followed by a prompt therapeutic response.[9] Presumably, this was brought about by (a) the diminution in peripheral resistance against which the failing ventricle was working, and (b) a shift of blood from the pulmonary parenchyma to the peripheral vascular bed as a result of the peripheral vasodilation. The use of peripheral vasodilation as a means of treating acute pulmonary edema has since received firm confirmation in laboratory experiments.[2–5] The fall in blood pressure following the spinal block in one patient was precipitous, however, and the patient became much worse in the few minutes before the therapeutic effect of the procedure set in. More recently, as little as 30 mg. of procaine in the third lumbar intercostal space provoked a drastic and sudden fall of arterial pressure from 180/100 to 60/35 mm. Hg within five minutes in a hypertensive patient.

The ganglionic blockade produced by Ro 2-2222, however, has distinct therapeutic advantages over spinal anesthesia. After producing severe arterial hypertension and pulmonary venous pressures up to 70 mm. Hg. by stimulating medullary cardiovascular centers,[2–5] Ro 2-2222 administration promptly lowered pulmonary venous pressure to control levels and significantly raised the cardiac output, but with only a slight or moderate lowering of peripheral arterial pressure. The effect was in sharp contrast to the often drastic and unpredictable fall in arterial blood pressure produced by spinal anesthesia. Phlebotomy, under the same experimental conditions, lowered pulmonary venous pressure, but failed to elevate, and occasionally even depressed, cardiac output.

It was largely with the acute pulmonary edematous state and the above experiences with spinal anesthesia in mind that a compound was sought which would provide a quantitative method of diminishing peripheral resistance in a gentler and more promptly controllable

manner than has been possible by other means. From the above data it appears that the continuous graded, intravenous administration of Ro 2-2222 furnishes such a method. The first case report cited above would seem to confirm the previous experimental data which relate peripheral vascular tone to the acute pulmonary edema state in hypertension.

The lack of a therapeutic effect in the second patient might be attributable to either (a) the fact that the pulmonary edema of uremia is not predominantly a result of increased pulmonary capillary pressure, (b) the fact that the peripheral vasomotor tone is not predominantly under neural influence but rather is a result of blood chemical changes, (c) the fact that the total peripheral arteriolar bed has been constricted by chemically irreversible organic vascular changes, or (d) inadequate dosage. It is apparent that more specific experimental data is needed regarding the mechanism of acute pulmonary edema in uremia.

The third patient with acute pulmonary edema had nearly normal blood pressure. Pulmonary edema occurred on the second hospital day following intensive fluid replacement therapy for shock and oliguria. The primary difficulty appeared to be a lower nephron nephrosis following exposure to a chlorinated hydrocarbon, with azotemia and hypochloremia severe enough to produce oliguria and severe hypotension. As the hypotension and oliguria were relieved by infusion of hypertonic saline and finally by 250 cc. of blood, congestive failure and acute pulmonary edema appeared. The extremities were warm and dry and the blood pressure 145/95. The liver was enlarged and tender, and there were rales as well as asthmatic wheezes throughout both lung fields, suggesting that hypervolemia was a major factor in producing the acute pulmonary edematous state. Again marked clinical improvement following injections of Ro 2-2222 were associated with a fall in peripheral arterial and venous blood pressure, relief of wheezing and orthopnea, and no significant change in pulse rate. It was not possible to judge whether the patient's azotemia played a role, per se, in producing pulmonary edema. The hemodynamic considerations regarding both pathogenesis and treatment by peripheral dilatation seemed to apply to this case of pulmonary edema in a normotensive individual fully as well as to the previous case with hypertension.

The depressor response to Ro 2-2222 in man, when given as a single intravenous dose, is brief. This characteristic of the drug, however, makes possible the prompt reversibility of the induced depressor reaction when given as a continuous infusion and thus facilitates the precise regulation of arterial pressure. If, as presumed, this graded reduction of arterial pressure is due to quantitative ganglionic blockade, the means is at hand for the continuous regulation of peripheral vascular resistance over a period of hours. Observations for more prolonged periods have not yet been made.

It seems appropriate to state why it seemed worthwhile to investigate the use of an agent which requires an intravenous drip for the best results in the therapy of what is frequently an emergency situation. This consideration becomes even more pointed in view of the similarity in the type and rapidity of relief obtained in the same patient treated with a continuous infusion of Ro 2-2222 on one day and on the following day with a single injection of protoveratrine. Although the patient's second attack of pulmonary edema was apparently not as severe as the previous one, the relief obtained with the single injection of protoveratrine closely resembled the result obtained with continuous infusion of Ro 2-2222. The reasons for preferring the continuous infusion method follow. They presume the desire to achieve the ideal rather than the approximate in the management of the acute pulmonary edematous state.

As suggested elsewhere,[2–5, 9] it is desirable to treat acute pulmonary edema by inducing peripheral vasodilation in order (a) to diminish the resistance against which the left ventricle is working and also (b) to decrease pulmonary blood volume by shifting blood into the peripheral vascular bed. However, there is reason to believe that in patients with hypertension and vascular disease, it is wise to avoid a sudden and drastic lowering of arterial pressure. Theoretically, at least, this revolves around the necessity of preventing a critical lowering

of perfusion pressure in the arteries leading to the heart, kidney, and brain. When a depressor agent is to be given as a single injection, selection of the dose in terms of the depressor response desired will require previous information regarding how much of that drug will achieve the desired depression in that particular patient. This is rarely available. On the other hand, when it is possible to titrate the response by regulating the rate of administration, such previous information is unnecessary.

Finally, in such normotensive individuals as case 3, where the choice is between pulmonary edema and shock, a well-known clinical dilemma exists in which customary measures aimed at treating pulmonary edema are apt to aggravate shock. In such situations one must walk a physiologic tightrope on which a readily reversible, quantitatively regulated agent has obvious advantages. That acute pulmonary edema associated with coronary insufficiency may be effectively treated by means of careful peripheral vasodilation is suggested by previous data on one such patient to whom spinal anesthesia was administered.[9]

Chronic toxicity studies on this agent have not yet been completed, and the number of patients who have received the drug is small. A prolonged clotting time is produced by large amounts of this substance in the dog, but not in the mouse, rat, rabbit, guinea pig, cat, or monkey.[1] Clotting times were not found to be elevated in the three patients in whom this determination was made after the administration of Ro 2-2222.

When Ro 2-2222 was administered at effective rates intravenously, most patients experienced a desire to yawn repeatedly. In two patients this was followed by actual nausea with retching or vomiting, of which yawning is a common symptomatic precursor. Both of these patients had already been chronically nauseated and vomiting intermittently because of advanced uremia, but there seemed to be little doubt that Ro 2-2222 accentuated this symptomatology. Accurate dosage regulation was apparently responsible for minimizing the undesirable gastrointestinal side effects so commonly observed with most depressor agents.

The apparent freedom from tachyphylaxis, insofar as determined by the above studies, suggests the possible use of this substance in the control of hypertension for longer periods than have been herein described.

The practice of maintaining low arterial pressures during surgery in order to diminish blood loss has been recently revived. Ro 2-2222 has the characteristics of an agent suitable for such a purpose since the degree of depressor response can be regulated from moment to moment and can be reversed readily in a controlled fashion. Under ether and cyclopropane anesthesia, the intraoperative arterial pressures have been lowered to and maintained at levels of 65/45 mm. Hg throughout the following four procedures: radical mastectomy (1), spinal cordotomy (1), and removal of large intracranial meningiomas (2). Intraoperative blood loss and postoperative transfusion requirements appeared to be materially diminished. The re-elevation of arterial pressure occurred as promptly in these four normotensive patients under anesthesia as in the patients described above following cessation of intravenous administration of Ro 2-2222. The results of further studies will be published subsequently.[18]

A full understanding of the mode of action and variety of effects of the ganglionic blocking agents is not yet at hand. In the dog, for example, tetraethylammonium does not block the pressor response to asphyxia, whereas in the cat it does.[10] Stone, Entwistle and Loew[11] have recently shown that tetraethylammonium causes the discharge of a pressor substance from the adrenal gland, and Reiser and Ferris[12] stated that tetraethylammonium produced a pressor rather than a depressor response in 6 of 20 hypertensive patients (30 per cent). A pressor response did not occur in any of the 14 hypertensive patients to whom Ro 2-2222 was administered. Recent work by Siems and Rottenstein[13] suggests that tetraethylammonium has an effect on the vascular bed, distal to the point of ganglionic blockade. The use of tetraethylammonium in man has suggested to Fowler and co-workers[14] that the drug has a direct cardiac effect, and Freis and associates[15] found that tetraethylammonium intensified the pressor effect of epinephrine and norepinephrine in man. That the situation is equally complex

in the case of the methonium compounds is suggested in the recent article by Paton.[16]

Mitchell and co-workers[17] have recently reported that Ro 2-2222 produces the liberation of histamine when administered to dogs. The characteristic flush and headache that accompany the presence of higher than normal blood levels of histamine in man have not been encountered in the above described series of patients. Further, from the data of Randall and colleagues,[1] the dog seems to react with a histamine response not observed in other species.

In view of the foregoing, the authors are keenly aware that, since a diverse body of information is not yet available in regard to Ro 2-2222 and clinical experience is limited to the studies presented herein, this report must be considered to be of a preliminary nature.

Summary and Conclusions

1. Ro 2-2222 in man produces a diminution in sympathetic activity, presumably by ganglionic blockade, which is evanescent in response to a single intravenous dose of 0.1 or 0.2 mg. per kilogram.

2. The depression of arterial pressure and rise in skin temperature responds in a satisfactory manner to various rates of administration when the continuous infusion technic is used. Either partial or apparently complete chemical sympathectomy can be achieved and a steady state maintained by regulation of the rate of administration of the agent.

3. The rate and the degree of sympathetic blockade achieved can be reasonably well controlled with minimal side effects so that either a precipitous or gentle lowering of arterial pressure results. On the basis of previous studies this suggests that the agent may be of use in the management of the acute pulmonary edema state.

4. Arterial pressure begins to return to control levels soon after discontinuance of the drug. Ephedrine is effective in elevating arterial pressure during the administration of the drug.

5. In the two patients so studied, the cold pressor test response was abolished during administration of Ro 2-2222.

6. Tachyphylaxis did not become apparent under the conditions of study observed above.

7. The results of treatment with Ro 2-2222 in three patients with acute pulmonary edema have been presented.

Addendum

Since this manuscript was submitted, the therapeutic effect of Ro 2-2222 upon acute pulmonary edema with essential hypertension has been confirmed in two additional patients, one of whom had not responded to intravenous morphine, oxygen by face mask, and tourniquets. Two patients with rheumatic valvular heart disease and mild pulmonary edema, but with normal arterial pressures, showed disappearance of orthopnea after slight peripheral vasodilatation with Ro 2-2222.

Three children, 8, 10, and 14 years of age, with hypertension accompanying acute glomerulonephritis, showed no fall in blood pressure following Ro 2-2222 administration, confirming the findings in our case report 2. One other patient in chronic pulmonary edema associated with severe uremia showed no clinical response to Ro 2-2222 even though reduction of arterial pressure was accomplished. One patient with acute pulmonary edema associated with a myocardial infarction did not respond in a convincing manner to Ro 2-2222. One moribund patient exhibited a sustained fall in cerebral spinal fluid pressure from 325 to 225 mm. of water, associated with a fall of arterial pressure from greater than 300/240 to 240/135 mm. Hg, and a fall of venous pressure from 315 to 165 mm. of water.

Three patients with acute bronchial asthma were not benefited by Ro 2-2222 administration, despite lowering of blood pressure, in contrast to the favorable effect of the drug in case 3 reported herein, in whom the asthma appeared to be on a cardiac basis. It is conceivable that this agent might occasionally be valuable in differentiating bronchial from cardiac asthma.

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On Certain Abnormal Ballistic Complexes: Their Relationships to Other Mechanical and Electrical Events of the Cardiac Cycle

By PETER T. KUO, M.D., D.SC. (MED.), TRUMAN G. SCHNABEL, JR., M.D., AND CALVIN F. KAY, M.D.

Ballistocardiograms were recorded simultaneously with intra-atrial and intra-aortic pressure curves, heart sounds, electrokymograms and electrocardiograms in patients with various types of heart disease. In several of these subjects, in addition to the usual ballistic waves, abnormal sets of ballistic complexes occurred. In some individuals, one or more of these abnormal ballistic complexes was so prominent that it dominated the entire ballistocardiogram. By correlating the abnormal ballistic waves with other dynamic and electrical events, we have secured information which throws light on the genesis of certain abnormal waves and of the so-called H wave in the ballistocardiogram.

BALLISTOCARDIOGRAMS of individuals with heart disease may show a wide variety of abnormalities. Starr, Hamilton, Nickerson, Brown, and others have described many abnormal ballistic patterns associated with various clinical entities.[1-15] The purpose of this study has been to establish a physiologic basis for some of these abnormal waves, by recording ballistic and other circulatory phenomena simultaneously.

MATERIAL AND METHOD OF STUDY

Recording Methods and Equipment. The ballistocardiographs used in this investigation were the original electromagnetic and the modified photoelectric (Sanborn) types developed by Dock and Taubman.[13] Through the courtesy of Dr. Isaac Starr, we were also able to obtain one to three tracings by the table ballistocardiograph[3] in each of our patients for comparative study. Ballistocardiograms taken with these three sets of instruments were found to check accurately in form and timing. Catheterizations of the right atrium and aorta were done by the small plastic catheter technic utilizing a Lilly capacitance manometer as described by Fitzpatrick, Schnabel, and Peterson.[16] The time lag of this arrangement was about 0.002 second. The electrokymographic equipment was of the type developed by Henny, Boone, and others,[17, 18] and manufactured by the Cambridge Instrument Company. The time lag of this instrument has been calibrated at 0.015 second with a frequency range of 1 to 35 cycles per second. The apex impulse was recorded by means of a glycerine capsule. The deflections were amplified through a Lilly capacitance manometer. The phonographic, lead II electrocardiographic, and other recordings were all taken on a Sanborn tribeam instrument with film speeds of 25 mm. and 75 mm. per second.

Technically, it was impossible to record all the hemodynamic phenomena simultaneously, and as a result, multiple recordings in various combinations of three were taken simultaneously with the phonocardiograph and/or the electrocardiograph. In order to avoid unnecessary repetition and confusion in presentation of the data, some of the illustrations were traced from the actual records with the electrocardiogram used for reference.

Selection of Patients. Subjects were selected in whom abnormal sets of ballistic waves could be isolated from each other and from the usually recorded waves by a distinct separation in time. Suitable examples were found in patients with the following types of disorders:

(1) Complete atrioventricular heart block with a slow ventricular rate. (2) Prolonged atrioventricular conduction time with presystolic gallop sound. (3) Congestive heart failure with presystolic gallop sound. (4) Constrictive pericarditis with a loud third heart sound in protodiastole. (5) Asynchronous ejections of the two ventricles. (6) Combinations of the above mentioned abnormalities.

Method of Study. All subjects had rested in the recumbent position for half an hour prior to the

From the Robinette Foundation, Medical Clinic, Hospital of the University of Pennsylvania. This study was supported in part by grants of the National Heart Institute, United States Public Health Service.

This work was done during the tenure of a Fellowship of the American Heart Association held by T.G.S., Jr.

Presented at the Twenty-Fourth Annual Scientific Sessions, American Heart Association, June 9, 1951, Atlantic City, N. J.

beginning of the study. They were instructed to stop breathing momentarily without straining, while the recordings were being made. Initially, a ballistocardiogram was obtained simultaneously with an electrocardiogram and a phonocardiogram. Examination of the preliminary tracings made it possible to determine the exact position of the abnormal ballistic complex in the cardiac cycle, and hence gave a clue to the origin of the hemodynamic impact. If such inspection showed that an abnormal ballistic complex appeared in diastole, at either the early or the late phase of ventricular filling, the right atrium was catheterized, and electrokymographic recording of the right ventricular border movements were made. If abnormal ballistic waves were present in systole, electrokymograms of the aortic and pulmonary arterial pulsations, as well as intra-aortic pressure curves, were taken. An apex impulse was recorded in all patients studied. In a few patients, studies of the mechanical events of both the right and left sides of the heart were made with catheterization and electrokymogram, on separate occasions, in correlation with the ballistocardiographic waves.

As an illustration of the recordings obtained in this study, figure 1 shows a normal ballistic complex from a healthy medical student, recorded simultaneously with heart sounds and electrocardiogram, at a film speed of 75 mm. per second. The usual H, I, J, K waves and the vibrations in diastole are clearly defined.

Results

Studies on Diastolic Ballistic Complexes. Diastolic ballistic complexes were seen in our subjects either following atrial contraction or in protodiastole. Patients with complete A-V heart block show small ballistic complexes following each atrial contraction.[3, 11, 19] Figure 2 is a record obtained from a patient with complete A-V heart block. It shows a series of small ballistic deflections in diastole and a faint atrial sound (A) following the P wave of lead II of the electrocardiogram. The systolic complex is essentially normal, except that no H wave is present.

That these ballistic complexes are related to atrial contractions can be seen in figure 3, which shows recordings obtained in another patient with complete A-V heart block. Figure 3*A* shows the relationship of the right atrial pressure curve to the P waves of the electrocardiogram. In figure 3*B*, the series of small ballistic deflections of atrial origin can be seen following the peaks of the right atrial pressure curve.

Figure 4 demonstrates the atrial origin of the H wave in a third patient with complete A-V heart block. This continuous tracing clearly shows that when the P-R interval is of normal duration, a small H wave is present in the ventricular ballistic complex. When the atrial and ventricular contractions are widely separated the series of small atrial ballistic deflections are evident and no H wave is seen in the ventricular ballistic complex.

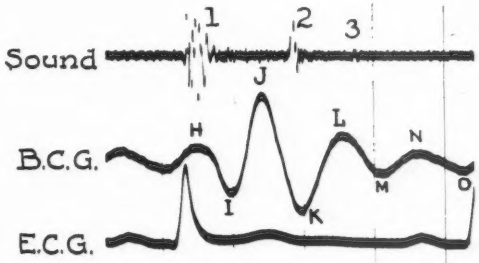

Fig. 1. Ballistocardiogram of a healthy medical student, taken simultaneously with phonocardiogram and electrocardiogram. Film speed 75 mm. per second.

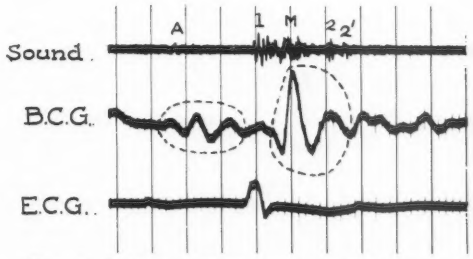

Fig. 2. Ballistocardiogram of patient S.Z. with complete A-V heart block, taken simultaneously with phonocardiogram and electrocardiogram. The atrial and ventricular ballistic complexes are circled in dotted lines. Film speed 25 mm. per second.

To further demonstrate the dynamic relation of atrial systole to the series of small diastolic ballistic deflections, studies obtained from patient J. C. with arteriosclerotic heart disease, congestive failure, prolonged P-R conduction time, and a presystolic gallop sound are shown in figure 5. The gallop sound could be heard, as shown in the sound record (G); and felt, as shown by a small presystolic thrust in the apex impulse recording. These events oc-

curred immediately after the peak of the right atrial pressure curve, and were thus associated with atrial contraction and ventricular filling.

The manner in which late diastolic ballistic movements followed the P wave of the electrocardiogram and the increase in pressure in the right atrium in our patient with presystolic

with the strength of the beat. It is interesting to note that the diastolic ballistic complex at the end of the first beat is larger than that of the following systolic complex. A presystolic gallop sound and a small presystolic apical thrust are present. The familiar series of small ballistic deflections follows the peak of the intra-atrial pressure curve in the usual manner.

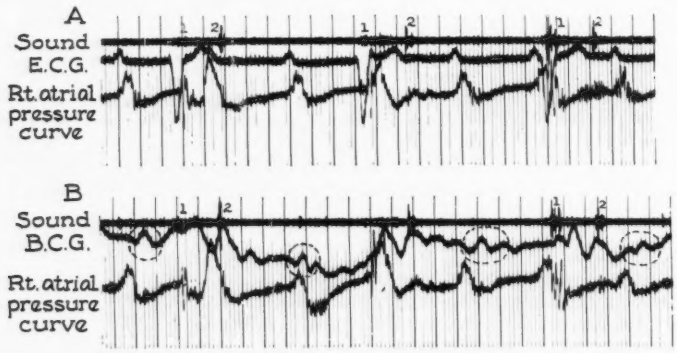

FIG. 3*A* AND 3*B*. Recordings obtained from patient C. J. with complete A-V heart block, showing relationships between the ballistocardiogram and the intra-atrial pressure curve and the electrocardiogram.

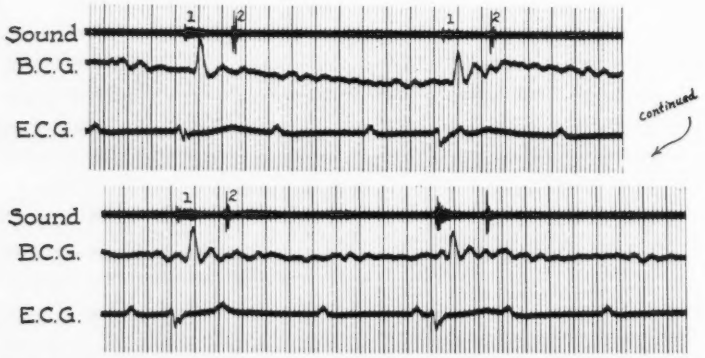

FIG. 4. Continuous tracing of patient L. K. with complete A-V heart block, showing the atrial origin of the H waves.

gallop rhythm is illustrated in figure 6. Patient W. S. had severe hypertension, complicated by congestive failure. He had a mechanical pulsus alternans as shown in the electrokymographic recordings of the left ventricular border and of the aorta. The first left ventricular contraction is more complete and results in a larger aortic pulsation than that of the second. The systolic ballistic complex is seen to vary in amplitude

The upward deflection of this complex, occurring just before the ventricular ejection, may be interpreted as an H wave. Mechanical alternans is not present in the right intra-atrial pressure curve or in the diastolic ballistic complex.

Figure 7 shows recordings made from patient J. M., who has chronic constrictive pericarditis. A loud third heart sound in early

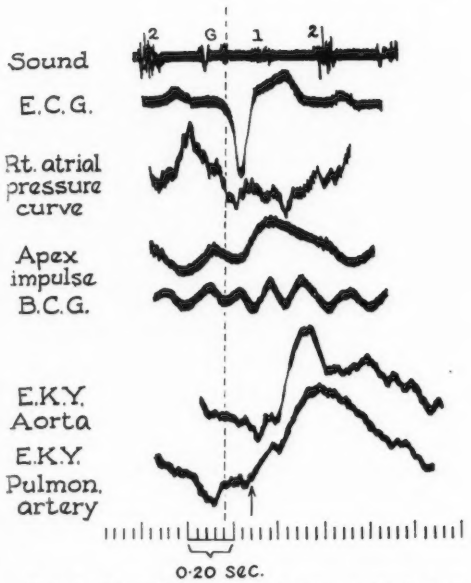

FIG. 5. Recordings obtained from patient J. C. with arteriosclerotic heart disease, prolonged P-R interval, left bundle branch block, and presystolic gallop rhythm. The arrow points to the onset of pulmonary arterial pulsation. The notch at the middle of the upward limb of the E.K.Y. is a distortion caused by the onset of the adjacant aortic pulsation.

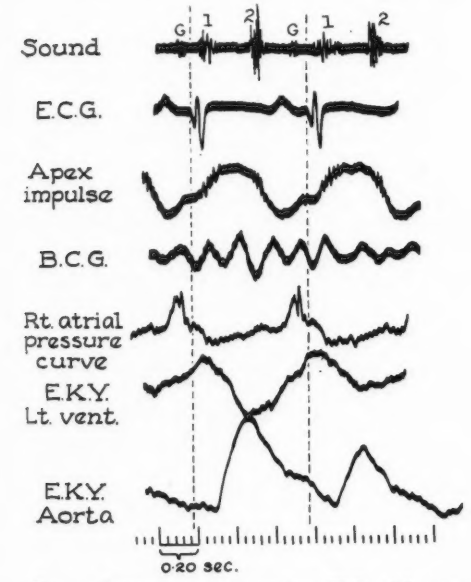

FIG. 6. Recordings from patient W.S. with severe hypertension, presystolic gallop rhythm, and mechanical pulsus alternans.

diastole (G) ("the diastolic heart beat")[22] is associated with an abrupt outward thrust of the apex impulse record, a rapid outward movement of the right ventricular wall as seen in the electrokymogram, and a rapid fall in the intra-atrial pressure. A series of small ballistic deflections very similar to those produced by active atrial contractions is seen to occur simultaneously with these events.

Studies on a Type of Abnormal Systolic Ballistic Complex. Figure 8 shows the studies made on patient M. R. She has congenital heart dis-

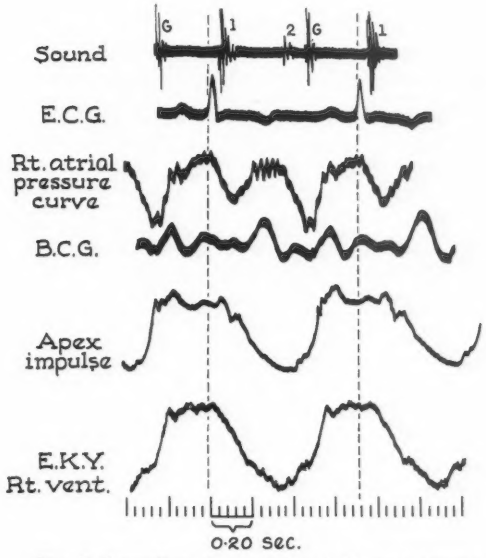

FIG. 7. Recordings from patient J. M. with chronic constrictive pericarditis, marked elevation of venous pressure, and a loud "diastolic heart beat" (G) in protodiastole.

ease with interatrial septal defect. The ballistocardiogram shows two upward deflections prior to the J wave; one before and the other after the onset of the QRS complex of the electrocardiogram. The upward deflection before the QRS complex is associated with a group of presystolic vibrations in the apex impulse record, and is probably atrial in origin. The ventricular ejections are not synchronous. A reduplication of both the first (1, 1′) and the second (2, 2′) heart sounds is recorded phonographically. The pulmonary arterial ejection curve precedes the aortic ejection curve of the electrokymogram

and the intra-aortic pressure curve. The apex impulse shows a group of larger vibrations at the beginning of the ventricular contraction. The second upward deflection in the ballistocardiogram is observed to start with the systolic apical vibrations, which occurs after the QRS complex of the electrocardiogram, and immediately after the onset of the pulmonary arterial ejection. Thus, in this tracing, two prominent upward deflections appear in the ballistocardiogram during systole, corresponding to the asynchronous ejections of the two ventricles.

Figure 9 was recorded from patient A. S. with rheumatic heart disease, mitral stenosis,

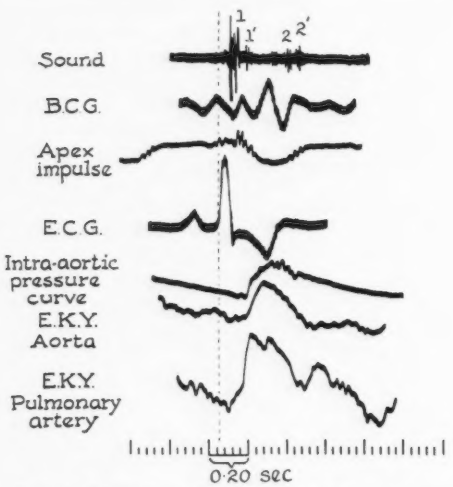

FIG. 8. Recordings from patient M.R. with congenital heart disease, interatrial septal defect, and splitting of the heart sounds.

and auricular fibrillation. An opening snap sound (o. s.) is recorded. The electrokymogram suggests that ventricular asynchronism is also present. The ballistocardiogram again shows two prominent systolic ballistic complexes. These complexes appear to correspond to asynchronous ejections of the two ventricles as shown by the electrokymographic recordings of the aorta and the pulmonary arterial pulsations. The first of these two upward deflections in the ballistocardiogram starts with the apical thrust and could be interpreted as an H wave.

The records obtained from the patient J. C. (presented above to show the association of prolonged P-R interval with a presystolic auricular ballistic complex), also shows an abnormal systolic ballistic complex (fig. 5). The electrocardiogram demonstrates a bundle branch block. Studies of the complete electrocardiogram show this to be of the left bundle branch block type. The illustration again shows asynchronism of the ventricular contractions as indicated by the electrokymographic studies. This phenomenon is accompanied by a bifid systolic complex in the ballistocardiogram.

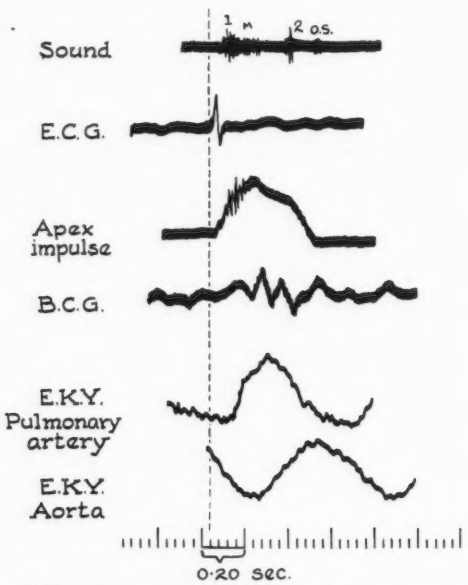

FIG. 9. Recordings from patient A.S. with rheumatic heart disease, mitral stenosis, and a loud opening snap sound (o. s.).

DISCUSSION

In the normal ballistocardiogram, the systolic excursion greatly exceeds the diastolic, so one can properly believe that the forces exerted by the many blood impacts in systole exceed those generated in diastole. However, in patients with heart disease, the hemodynamic forces other than those which are produced by the main ventricular contraction may become quite prominent. For this reason, ballistocardiograms of these individuals may show in addition to the usual ballistic waves, one or more sets of abnormal ballistic complexes. Sometimes, such

complexes may be large enough to dominate the entire ballistocardiogram. An understanding of the physiologic basis of these abnormal ballistic complexes is important in the interpretation of the abnormal ballistocardiograms.

The diastolic waves seen in the ballistocardiogram have aroused much interest and speculation. Hamilton and his associates[2] believed that the L, M and N waves are related to waves oscillating back and forth in the ascending aorta. The O wave was thought to have its origin in the reflection of the pressure wave at the arterioles in the lower part of the body. On the other hand, Starr and Mayock[10] in their study of abnormal ballistocardiograms, contended on clinical grounds that large diastolic waves were probably produced by a sudden inrush of blood into the heart under certain pathologic conditions. More recently, Dock and Taubman[13] reported large L, M, and other diastolic waves in patients with rheumatic carditis and in other disease conditions where the rate of return of blood into the ventricles was thought to be increased and rapid. We are able to demonstrate diastolic complexes associated with gallop rhythms, which seem to favor the views held by Starr and by Dock and their associates. The series of small diastolic ballistic deflections produced by passive ventricular filling may be regarded as a factor in the formation of the terminal portion of the ascending limb of the L wave, and the M, N, O vibrations in the ballistocardiogram seen in the early part of the diastole in certain individuals. This belief is strengthened by our observation that these "after vibrations" in ballistocardiograms taken on healthy individuals with a loud third heart sound (fig. 1), are usually very well defined and prominent. Studies of the circulatory dynamics of these healthy individuals indicate that ventricular filling is completed in a short space of time in early diastole, and that ventricular ejection is forceful.

The ballistic waves of atrial origin were first reported by Starr and Schroeder,[3] and an analysis of these waves in patients with complete A-V heart block was made by Nickerson.[11] He felt that the first atrial ballistocardiographic deflection was upward and labeled it H. Recently, de Lalla, Epstein, and Brown[19] reported similar diastolic patterns of atrial origin, but differed with Nickerson in believing that the first atrial ballistocardiographic deflection was in a downward direction, and was probably related to deceleration of blood and impulse wave by the ventricles. This deflection (G) was found to come immediately after the small upward wave labeled H by Nickerson. Dock and Taubman[13] also observed deep downward ballistic waves due to deceleration of blood in diastole, in patients with protodiastolic and presystolic gallop rhythms. This study, however, shows that the diastolic ballistic complexes resulting from atrial systoles, and those occurring in individuals with protodiastolic and presystolic gallop rhythms are very similar to one another. These complexes usually consist of a series of small deflections. It is often difficult to determine which one of the waves is the initial deflection. Furthermore, it is possible to reproduce almost identical diastolic ballistic complexes in individuals with bradycardia, by tapping gently on the shoulder, and thereby imparting a tiny footward movement of the body. These findings lead us to believe that those forces resulting from atrial systole and/or ventricular filling lack the abruptness necessary to cause one clearly defined deflection in the ballistocardiogram.

Currently, there is some difference of opinion in regard to the origin of the H wave. Starr and Schroeder,[3] and Hamilton[2] related the beginning of cardiac movements in isometric contraction to the H wave. Nickerson,[11] however, showed that when atrial contraction is in normal temporal relation to ventricular contraction, the H wave is produced by the initial upward ballistic deflection of the atrial ballistocardiogram. Because H waves may be seen in some cases of auricular fibrillation, de Lalla and his associates[19] concluded that the H wave represents a force produced by the apex thrust as well as by atrial contraction. This study shows that any one of the upward deflections in the atrial ballistocardiogram may form the H wave. Whether the H wave is caused by the initial upstroke of the diastolic ballistic complex or another of its upward components will depend upon the duration of the P-R interval.

In the cases we have studied, the H wave was found to start at the time of the apical thrust when the P-R interval was within normal limits. The so-called H wave sometimes seen in patients without active atrial contraction, as in auricular fibrillation, can be properly attributed to ballistic waves caused by asynchronous ejections of the ventricles.

It is of interest to note that the double peaked systolic ballistic complexes have been encountered almost exclusively in patients in whom the pulmonary arterial ejection precedes that of the aortic. A combination of early pulmonic ejection and right ventricular hypertrophy is found to give a maximum ballistic effect. When the right ventricular ejection happens to lag behind the left ventricular ejection, the relatively weak ballistic result is usually lost in the main ballistic complex of the left ventricular contraction and ejection of blood into the aorta. This observation could very well explain why "many cases of bundle branch block have normal ballistocardiograms."[10]

The present study naturally raises the question of the quantitative distorting influence of the ballistic waves of atrial systole, ventricular filling, ventricular asynchronism, and waves of other undetermined origin upon the amplitude of (I + J) in both normal and abnormal conditions. The degree of any such influence would proportionately limit the usefulness of the measurement of these waves as an index of velocity of systolic ejection[20] and of cardiac output.[1, 21] Further studies should be designed to provide a satisfactory answer to this important question.

Summary

1. A correlated study of ballistocardiograms with electrical and mechanical events of the cardiac cycle has been made on patients with various types of heart disease.

2. The results obtained from this study show: (a) A rapid, forceful diastolic ventricular filling wave occurring either in protodiastole or in presystole can account for large diastolic ballistic waves seen in an abnormal ballistocardiogram. Diastolic apical thrust and gallop sound are usually present.

(b) Atrial systole causes a series of small ballistic deflections. When the P-R interval is of normal duration, part of this complex produces an H wave in the ballistocardiogram, which usually begins at the time of the apical thrust.

(c) In some cases, waves which might be interpreted as H waves are seen in the absence of active atrial contraction, as in cases of auricular fibrillation. These H waves can be attributed to asynchronous ejections of the ventricles.

3. It is evident that the abnormal ballistic complexes may either increase or decrease the amplitudes of the H, I, J waves in the ballistocardiogram, thus limiting the value of using the I + J stroke for the estimation of cardiac output and the velocity of systolic ejection. In certain cases, the abnormal ballistic waves may even distort the whole ballistocardiogram making its interpretation exceedingly difficult.

Addendum

Since this paper was submitted for publication, we have observed two upward ballistic deflections during systole in patients with a significant degree of mitral insufficiency. The first of these two upward deflections could be interpreted as an H wave in such patients with auricular fibrillation.

Acknowledgment

The authors wish to acknowledge the help of Dr. Isaac Starr for his many helpful suggestions in the course of this investigation and the preparation of this manuscript.

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The Effect of Mercurial Diuretics on the Excretion of Water

By J. N. Capps, M.D., W. S. Wiggins, M.D., D. R. Axelrod, M.D., and R. F. Pitts, M.D.

In experiments on 11 normal subjects and on three dogs it has been observed that mercurial diuretics do not prevent the stimulation of water absorption and formation of hypertonic urine which characteristically follows the infusion of Pitressin. Furthermore mercurial diuretics only rarely increase urine flow when administered in the course of maximal water diuresis. These two facts are interpreted as meaning that the diuretic agents have no primary effect on the reabsorption of water. Rather, increased urine flow results secondarily from increased elimination of ions.

IN THE treatment of edematous patients, dosage and frequency of administration of mercurial diuretics are customarily gaged by weight loss. Such loss of weight represents largely loss of water from the extracellular fluid compartment. Although it is generally conceded that mercurial diuretics block some fraction of the renal tubular absorption of sodium and chloride, no conclusive evidence exists of whether or not they affect the absorption of water directly.[1] It is possible that loss of ions obligates in some way the excretion of equivalent quantities of water. On the other hand, renal tubular absorption of water per se might be inhibited to some extent by the diuretic agent. The present investigation was undertaken to provide experimental evidence on this point.

According to present concepts, large quantities of fluid, approaching 160 liters per day, are filtered through the glomeruli of normal man.[2] Ordinarily all but one or two liters are absorbed as the filtrate progresses through the renal tubules. The absorption of the major fraction of this water, up to 140 liters per day, is presumed to occur passively in the proximal segment in consequence of the active absorption of salts, glucose and other valuable constituents from the tubular fluid.[3] The absorption of these solutes, especially ions, is thought to establish the osmotic force which returns water to the blood stream. The absorption of the remainder of the water, up to 20 liters per day, is presumed to occur in more distal portions of the nephron, either in the distal segment of the renal tubule or in the collecting duct. The absorption of this moiety is independent of the absorption of solutes. At least solutes may be absorbed without the absorption of equivalent quantities of water and to some extent water may be transported actively, independently of solutes, and against an osmotic gradient. Two major factors condition completeness of absorption in this distal portion of the nephron* and hence final urine volume: (a) the concentration of circulating posterior pituitary antidiuretic hormone; and (b) the load of osmotically active solutes demanding excretion.[1]

It is possible that mercurial diuretics might depress the absorption of water, increase urine volume and reduce body weight in any one of three ways: (a) they might interfere directly with the mechanism for the active transport of water in the distal segment; (b) they might depress the proximal absorption of ions and hence interfere with the passive absorption of water; (c) they might increase the urinary load of solutes by depressing either the proximal

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* Hereafter we shall refer to the distal portion of the nephron as the distal segment, recognizing that in reality the exact morphologic segment is undetermined.

or distal absorption of ions, and hence impose an osmotic limitation on the active absorption of water in the distal segment.

Our method of approach in attempting to distinguish between these possibilities has been to hydrate our experimental subjects and animals in a fashion calculated to establish and maintain as high rates of urine flow as possible. We assume under these conditions that the secretion of posterior pituitary antidiuretic hormone has been inhibited and that little if any water is absorbed in the distal segment. The urine formed under these circumstances is quite hypotonic to the plasma. If the administration of a mercurial diuretic were to prevent the increased absorption of water and the formation of hypertonic urine which ordinarily attends the infusion of Pitressin, we would infer that the agent has interfered with the distal tubular absorption of water, namely that moiety regulated by the posterior pituitary mechanism. The fact that it does not inclines us to the view that a mercurial diuretic does not primarily influence the mechanism for the distal transport of water. If, under these conditions of maximal hydration, the administration of a mercurial diuretic were to increase urine flow in proportion to the increase in salt excretion, we would infer that the agent had blocked the active proximal absorption of ions and hence interfered indirectly with the passive absorption of water in this segment. Although our experiments have not been completely consistent, a majority suggest that mercurial diuretics do not primarily influence the proximal absorption of water. We have been forced by exclusion to the view that the increase in urinary osmotic load which results from blockage of ion absorption restricts the distal absorption of water and hence increases urine flow. Our results are most readily interpreted on the assumption that a mercurial diuretic blocks the distal absorption of ions.[4] It is also probable, although our experiments were not designed to test the point, that the dilution of the plasma which results from the loss of ions inhibits the secretion of antidiuretic hormone and thus reduces the activity of the distal mechanism of water absorption.

Methods

This report is based on 26 experiments performed on 11 adult male subjects and on three dogs. Nine of the 11 subjects were convalescent patients from the wards of the University Hospital. The other two were laboratory workers. None of these individuals exhibited any evidence of cardiovascular or renal disease. Two of the dogs were normal mongrel females; one had diabetes insipidus produced by stalk section.* All experiments were performed without anesthesia or sedation.

The human subjects were water loaded by the administration of two liters of tap water, ingested usually over a two-hour period from 7 to 9 a.m. Thereafter, every 20 minutes for the duration of the experiment, urine was voided and a volume of water was ingested equivalent to the volume of urine excreted. We were forced to discontinue a number of experiments because of nausea and vomiting or failure to establish a high urine flow.

Attempts to hydrate animals by repeated administration of water by stomach tube were unsuccessful. Passage of the tube was followed almost invariably by a sharp drop in urine flow during some phase of the procedure. The intravenous infusion of distilled water at rates of 10 to 12 cc. per minute invariably resulted in progressive hemolysis. The procedure finally adopted was to administer by stomach tube 500 to 800 cc. of water at the start of the experiment and to infuse intravenously, at a rate equivalent to urine output, a 2.5 per cent solution of glucose in distilled water. During the three to five hours required for the performance of an experiment, little or no glucose appeared in the urine.

The inulin clearance was used as a measure of glomerular filtration rate in man. The creatinine clearance was used in the dog. In both, the para-aminohippurate clearance at low plasma levels was used as a measure of minimum effective renal plasma flow. The osmotic concentrations of plasma and urine were determined by freezing point depression and are expressed in terms of "effective osmolarity," that is, values have not been corrected for activity. Methods employed are described in other communications.[5-7]

Results

An experiment on a dog with diabetes insipidus which illustrates the basic elements of the thesis we wish to present is summarized in table 1. In this experiment the animal was

* We are indebted to Dr. Allen D. Keller of the Medical Department, Field Research Laboratory, Fort Knox, Kentucky, who kindly prepared three diabetic insipidus animals for us. Unfortunately two were lost in early laboratory accidents.

water loaded and after the urine flow appeared to have stabilized near 10 cc. per minute, three control urines were collected. Eighty mg. of mercury as Mercurin* were then administered intravenously and five additional clearance observations were made. During the remainder of the experiment, Pitressin was infused at a rate of 250 milliunits per hour. After three more collection periods to determine the effects of Pitressin, 1 cc. of BAL was given intramuscularly to inhibit the action of the diuretic. A final series of three clearance periods permitted an assessment of the action of Pitressin in the absence of mercurial diuresis.

The peak urine flow attained during the control periods of this experiment amounted to 10.75 cc. per minute. Although this animal had diabetes insipidus of at least moderate severity,* some variability of urine flow under constant hydration was observed, not only in this, but in other experiments as well. However, with the exception of the second period after the administration of 80 mg. of mercury as Mercurin, urine flow remained below the average of the values established during the control periods. Since this animal in other experiments exhibited control urine flows as high as 13.5 cc. per minute, we feel that an increase to 11.6 cc. per minute has little significance with respect to the action of mercury. With the infusion of Pitressin, urine flow dropped progressively to reach a value of 1.24

TABLE 1.—*An experiment on a dog with diabetes insipidus which illustrates the fact that mercurial diuretics do not specifically block the absorption of water, but rather that they block ion absorption and secondarily impose an osmotic limitation on the absorption of water.*

Time	Urine Flow	Glom. Filt. Rate	Renal Plasma Flow	Plasma				Urine Conc.	Rate of Excretion			
				Na	Cl	K	Conc.		Na	Cl	K	Osmotic Load
Min.	*cc./min.*			*mEq./L.*			*m.osmols/L.*		*μEq./min.*			*m.osmols/min.*
0–20	10.75	85.4	286	141	111	2.87	283	23	56	63	17	0.252
20–40	9.60	85.6	286	138	110	2.66	285	31	24	29	9	0.297
40–60	7.90	81.9	256	139	108	2.62	272	43	6	6	4	0.336
80 mg. Hg as Mercurin, intravenously												
60–80	8.50	84.7	194	137	106	2.58	270	42	58	42	17	0.357
80–100	11.65	84.9	194	136	105	2.87	272	121	500	495	36	1.410
100–120	9.51	72.8	184	134	103	2.83	258	105	372	388	29	1.000
120–140	7.29	69.4	183	133	103	2.87	244	129	152	158	19	0.942
140–160	7.90	72.7	208	132	101	2.70	243	153	174	175	20	1.208
250 milliunits Pitressin per hour added to infusion												
160–180	7.40	72.0	224	130	96	2.54	242	198	180	202	27	1.465
180–200	3.00	74.2	214	129	94	2.62	240	323	236	181	44	0.966
200–220	1.24	72.3	209	126	93	2.58	240	546	128	110	24	0.677
1 cc. BAL, intramuscularly												
220–240	0.60	62.8	165	128	90	1.90	240	545	97	68	5	0.327
240–260	0.63	71.9	167	130	92	1.55	242	414	3	1	5	0.262
260–280	0.60	67.0	167	132	93	1.50	242	631	3	0	9	0.379

* Mercurin was supplied through the courtesy of the Campbell Products, Inc., New York. Most of our experiments were performed with this product to avoid the complicating factor of the action of the theophylline contained in the commonly used mercurial diuretics.

* The 24 hour fluid output varied between 4 and 6 liters.

c. per minute. Following BAL it dropped till further to 0.6 cc. per minute.

The urine formed during the control periods was dilute. Although osmolarity increased following the administration of Mercurin due largely to increased excretion of sodium and chloride* ions, the urine remained hypotonic to the plasma. Following Pitressin, osmotic pressure† of the urine rose promptly, exceeding that of the plasma during the ninth and tenth periods. In fact, during the tenth period the total effective osmotic concentration of the urine was more than double that of the plasma. The fact that the urine flow diminished only to 1.24 cc. per minute is no doubt a consequence of the large load of osmotically active material presented for excretion. The lower urine volume and somewhat higher osmotic pressure after BAL is probably a consequence of the reduced osmotic load of sodium and chloride attained once the action of the mercury had been abolished.

We interpret this experiment to mean that a dose of 80 mg. of mercury, roughly 4 mg. per kilogram body weight, or four times the normal therapeutic dose in man, does not block the active distal tubular absorption of water, for it does not prevent the establishment of a high osmotic gradient between urine and plasma when Pitressin is infused. Identical results were obtained in another experiment in which a dose of 8 mg. of mercury per kilogram of body weight were administered. In line with this view is the statement of Gilman and Kidd[9] that "mercurial diuretics, even when increasing diuresis rate by 300 per cent, do not lower the osmotic ceiling for NaCl."

Two of four experiments on man, which are subject to similar interpretation, are summarized in figure 1. These individuals were hydrated in the standard fashion outlined in the section on methods. Mercurin in a dose of 80 mg. of mercury per kilogram was administered intravenously some 60 to 210 minutes prior to the start of the experiment. After two control periods a prime dose of 30 milliunits of Pitressin was given intravenously and the hormone was infused thereafter at a rate of 100 milliunits per hour. Urine flow, which varied between 13 and 20 cc. per minute during the control periods, dropped sharply following the administration of Pitressin to values between 1 and 3 cc. per minute. It is true that this Pitressin-induced antidiuresis was less striking after a mercurial diuretic than in a normal untreated subject. This we interpret to be a consequence of the large quantities of osmotically active electrolyte which appeared in the urine after mercury and which must have obligated the excretion of the water. Thus the urine which had been hypotonic to the plasma during the control periods became markedly hypertonic to the plasma after the administration of Pitressin, a fact which indicates that the characteristic action of the hormone in stimulating water absorption was not abolished by the mercurial diuretic. Furthermore, the lower the urinary osmotic load of solutes, largely sodium and chloride, the lower the urine flow following Pitressin, that is, the less the osmotic effect of these solutes in abstracting water from the body.

These experiments on man confirm the observations on the dog that the administration of a mercurial diuretic does not block the active tubular reabsorption of water, for it does not prevent the establishment of a high osmotic gradient between urine and plasma when Pitressin is infused. The fact that the

* The rates of sodium excretion which we have observed during mercurial diuresis under conditions of marked hydration have been rather low in comparison with those described in previous experimental work.[4] At least two factors must have played some role in reducing salt loss in these studies. It is evident from table 1 that the plasma concentrations of sodium and chloride dropped progressively throughout the course of the experiment. In addition, the rate of glomerular filtration declined after the fifth clearance period. Both factors operate to reduce the filtered load of ions, a circumstance which has previously been shown to reduce the efficacy of mercurial diuretics.[8]

† Osmotic concentrations in table 1 and figures 1 through 5 are expressed in terms of "effective osmolarity" in milliosmols per liter, calculated as $1000 \times \frac{\Delta E}{1.86}$, uncorrected for activity. Osmotic load is expressed in milliosmols per minute, calculated as the product of urine flow and urine osmotic concentration, divided by 1000.

urine flow after Mercurin cannot be reduced to as low a level as in the normal subject is no doubt correlated with the greater load of

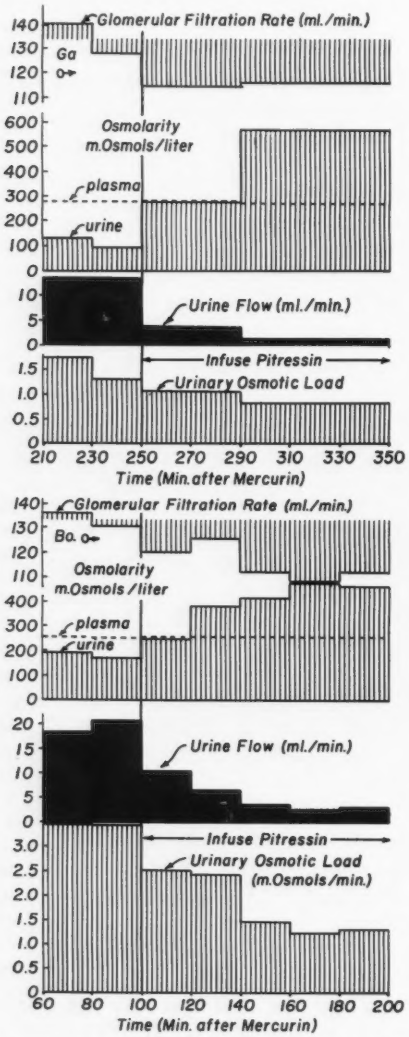

FIG. 1. Experiments on two normal subjects during mercurial diuresis illustrating their capacity to form urine hypertonic to plasma when infused with Pitressin.

osmotically active materials, chiefly sodium and chloride, demanding excretion.

Although these experiments are fairly conclusive in ruling out a direct action of mercurial diuretics on the active distal tubular absorption of water, and although they suggest that the increased flow of urine may be a consequence of the increased osmotic load presented to the distal tubule, they do not rule out the possibility that the excess water excreted might actually be derived from the proximal segment of the renal tubule. If mercurial diuretics were to block some fraction of the proximal tubular absorption of sodium and chloride ions, an extra amount of water would be delivered into the distal segment. This extra water might well account for the increase in urine flow.

An experiment designed to test this hypothesis is presented in figure 2. This experiment was performed on a normal dog, hydrated

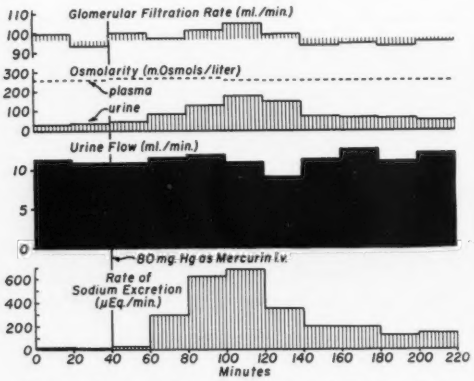

FIG. 2. An experiment on a normal dog in which a large dose of Mercurin, administered during so-called maximal sustained water diuresis, did not significantly increase urine flow.

according to the standard procedure. Following two control periods during which the urine flow averaged 11.1 cc. per minute, 80 mg. of mercury as Mercurin were given intravenously. During the succeeding three hours, urine flow varied only between limits of 8.9 and 12.6 cc. per minute. Such changes as were observed were in no way correlated with the fairly marked changes which occurred in the rate of excretion of sodium. This experiment was a fortunate one, for glomerular filtration rate remained very constant throughout.

Eight experiments in all, including four on normal dogs and four on the diabetes insipidus dog, yielded results in close agreement with those presented in figure 2. Although urine flow

and glomerular filtration rate varied considerably more in the experiments on the diabetes insipidus dog than in the ones on normal dogs, in no instance did urine flow after Mercurin appreciably exceed the maximum value established during the control periods. Furthermore, there was no evident correlation between the rate of excretion of water and the rate of excretion of sodium. However, there may well be some correlation, imperfect though it may be, between the rate of glomerular filtration and the rate of urine flow. In general, urine flow tended to be lower in those periods in which filtration rate was most reduced. However, in two experiments on one dog, increases

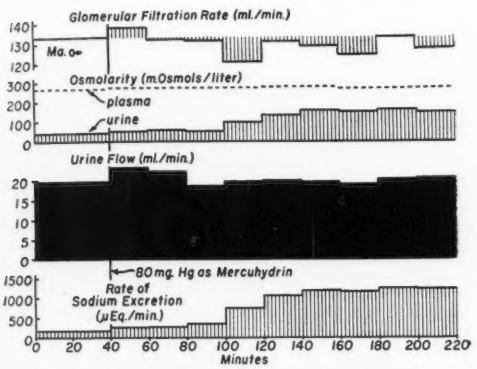

FIG. 3. An experiment on a normal subject in which a therapeutic dose of Mercurin, administered during so-called maximal sustained water diuresis, did not significantly increase urine flow. Similar results were obtained in two additional subjects.

in urine flow from 9 to 13 and from 11 to 14 cc. per minute were observed following the administration of Mercurin. In both instances the rate of glomerular filtration was appreciably increased above the control level during the periods of increased urine flow. Urine flow appeared to correlate somewhat better with filtration rate than with sodium excretion.

In figures 3 and 4 are presented results obtained in similar experiments on two convalescent patients. In the experiment on Ma., figure 3, control urine flow averaged 19.5 cc. per minute. Following 80 mg. of mercury as Mercuhydrin, urine flow rose to 23.1 cc. per minute but rapidly returned to the control levels. The increase in urine flow was obviously unrelated in this experiment to the increase in the rate of excretion of sodium induced by the mercurial diuretic. Filtration rate remained fairly constant near control values. In contrast, in the experiment on Va., figure 4, control urine flow averaged 15.5 cc. per minute (somewhat below the expected maximal rate), increased promptly to 23.5 cc. per minute after 160 mg. of mercury as Mercuhydrin, dropped briefly and then rose gradually to a peak of 27.9 cc. per minute at the time that the peak rate of sodium excretion was attained. In this experiment a very real increase in urine flow occurred which correlated well in the

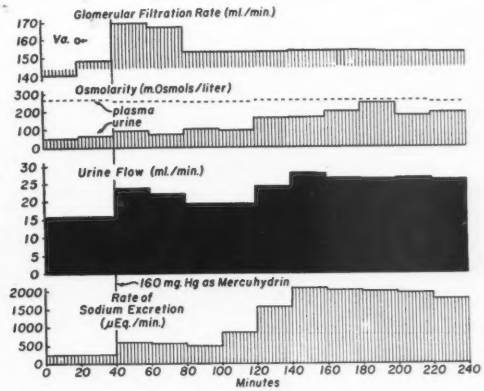

FIG. 4. An experiment on a normal subject in which a large dose of Mercuhydrin, administered during so-called maximal sustained water diuresis, significantly increased urine flow. Similar results were obtained in two additional subjects to whom therapeutic doses of Mercurin were administered.

later stages with the increase in rate of sodium excretion. However, it is possible that the marked and sustained increase in glomerular filtration rate may have been responsible in some way for the increase in urine flow. In all, six experiments of this type have been performed on human subjects. Three have followed the pattern outlined in figure 3, in which no significant increase in urine flow was observed following the administration of a mercurial diuretic. The other three followed the pattern outlined in figure 4. A significant increase in urine flow over and above the control level was observed in these instances. In all, some correlation could be established be-

tween urine flow and glomerular filtration rate. However, from the data available it is impossible to quantitate in any exact fashion the effect of a given increase in glomerular filtration rate on urine flow. In fact, it is even impossible to prove conclusively that a cause and effect relationship exists between these two variables.

Discussion

The data presented above establish the fact that a full therapeutic dose of a mercurial diuretic in man, or as much as eight times this dose per kilogram body weight in the dog, does not prevent the stimulation of the active absorption of water and the formation of hypertonic urine which normally follows the infusion of Pitressin. Although urine flow is not reduced to as low levels by Pitressin after a mercurial diuretic as before, the limiting factor appears to be the increased load of osmotically active materials demanding excretion rather than some primary effect of mercury on the water absorptive mechanism. In the presence of a large load of urinary sodium and chloride the kidney is unable to concentrate to as great a degree or to restrict flow to such low values as it can if the load is small.[9] These results are consonant with the view that mercurial diuretics do not interfere with the active absorption of water in the distal tubule, that is, that moiety subject to control by Pitressin.

It has been somewhat less conclusively established that a mercurial diuretic does not block the passive absorption of water in the proximal tubule. In the majority of the dog experiments and in half of the experiments on man our findings support this view. However, in two dog experiments and in three experiments on man, urine flow increased more or less in proportion to sodium and chloride excretion after the mercurial diuretic. This finding might be interpreted as favoring the concept that mercury inhibits the proximal absorption of sodium and chloride and hence indirectly inhibits the passive absorption of water. However, in each instance glomerular filtration rate increased. We favor the concept that the increase in urine flow is related in some fashion to the increase in filtration rate in these later experiments, rather than to blockage of the proximal absorption of fluid. However, we recognize the fact that this view has not been firmly established.

If mercurial diuretics do not primarily affect water absorption in either the proximal or distal tubule, the increase in urine flow and the loss of weight which accompanies successful therapy must be assigned in one way or another to osmotic forces. Blockage of ion absorption (the majority of our data favor the view of distal blockage) delivers increased quantities of osmotically active solutes into the urine, hindering thereby the active absorption of water in the distal segment. In addition, primary loss of ions might be expected to reduce the osmotic pressure of the body fluids, inhibit the secretion of Pitressin and permit an increased flow of urine.

Conclusions

Mercurial diuretics do not interfere with the active distal tubular absorption of water, that is, that moiety subject to control by Pitressin. It is suggested that the increased load of ions demanding excretion imposes an osmotic limitation on the active absorption of water in this segment, or in other words, osmotically abstracts water from the body. In addition the primary loss of ions might be expected to dilute the body fluids, inhibit the secretion of Pitressin and reduce the activity of the Pitressin-sensitive mechanism of water absorption. From the data available it is impossible to state definitively whether or not mercurial diuretics affect the passive proximal tubular absorption of water.

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The Circulatory Effects of Roniacol

A Physiologic Study in Normal Man

By G. S. Roback, M.D., M.S., and A. C. Ivy, Ph.D., M.D.

The vasodilatory effects of nicotinic alcohol tartrate (Roniacol) were tested on 12 normal adult males, utilizing digital venous occlusion plethysmography, brachial and digital artery oscillometry and flicker photometry. Orally administered Roniacol in single doses up to 200 mg. has no significant effect on the auscultatory blood pressure, pulse rate, or peripheral arterial circulation of normal individuals.

THERE ARE numerous pathologic conditions having as a common factor arterial insufficiency. These are mainly due to partial or complete reduction in arterial or arteriolar luminal size. This decrease is usually due to organic changes in the vessels, abnormal increase in the sympathetic vascular tone, or a combination of the two.

Various methods have been used in an attempt to increase the arterial blood supply. Locally acting agents and agents that act by the decrease of sympathetic vasular tone have been tried in an attempt to increase the functional vessel size or to increase the collateral circulation by maximal vasodilatation.

Temporary subjective improvement of peripheral arterial insufficiency has frequently been associated with the use of a new drug or type of treatment. The typical clinical course, however, is improvement for only a short period of time; either the basic pathologic processes progress, or the psychologic amelioration disappears, and the patient returns to the former status, or is frequently worse.

In order to determine objectively the effects of various drugs or treatments on the changes in peripheral arterial circulation in the human, various methods have been used. The most common have been: (1) variations in skin temperature, (2) exercise tolerance, (3) venous occlusion plethysmography, and (4) oscillometric volume fluctuations of the major or smaller vessels.

Skin temperature changes, being a measure of the skin circulation only, give only a suggested interpretation of the actual circulation in the deeper structures. Normal ranges of skin temperature have been demonstrated in individuals with markedly impaired muscular circulation.[1]

Exercise tolerance, although frequently an excellent index of muscular anoxia in the lower extremities, is too greatly related to the psychologic situation to serve as more than a clinical test for individual responses. It can not be considered reliable for the purpose of investigation of the physiologic effects of vasodilator drugs or new types of treatment unless continued over long periods of time. Many initial reports of effective vasodilator drugs have proved disappointing after prolonged trial where too much significance has been placed on the initial subjective improvements.

Venous occlusion plethysmography[1, 2] and oscillometry[3] have proved to be reliable means of measuring peripheral circulatory changes.

The flicker fusion threshold has been previously shown to be a reliable and sensitive indicator of the depressing action of anoxia and to reflect the generalized vascular response to vasodilators by alteration in the flicker fusion threshold. In the normal individual, vasodilation has been shown to produce a depression of the flicker fusion threshold by congestion and relative anoxia of the visual apparatus. In the vasospastic individual there is an increase of the flicker fusion threshold by removing the spasm and thus increasing the blood supply.[4]

Digital venous occlusion plethysmography, brachial and digital artery oscillometry, and flicker photometry were utilized in this study.

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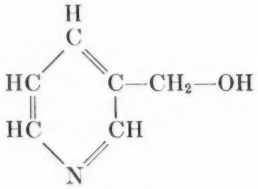
Purpose

The purpose of this investigation has been to evaluate the vasodilatory effects of Roniacol* (nicotinic alcohol tartrate). Numerous clinical evaluations of this drug have been made, with rather consistently favorable vasodilatory results reported.[5-7] Roniacol has been reported as having a vasodilatory effect on both coronary and peripheral circulation.[8]

However, clinical evaluation has been made on a purely subjective level without measurement of changes in actual circulatory volume.

Chemical Properties of Roniacol

Roniacol is a 3-pyridine-methanol or β-pyridyl-carbinol (the alcohol corresponding to nicotinic acid) with the following structural formula:



It is a nonvolatile colorless liquid with a slight characteristic odor and is freely soluble in water and alcohol. Aqueous solutions are practically neutral.[9]

Procedure

Materials. All oscillometric and venous occlusion plethysmographic determinations were made with the Johnson Recording Oscillometer,[10] a simple apparatus recording the peripheral volume pulse wave on photographic paper. It consists of a reinforced blood pressure cuff that is applied around the appendage to be measured. The greatest systolic amplitude of the peripheral volume wave is determined from tracings taken at each 5 mm. Hg occlusion pressure level from 20 mm. above auscultatory systolic pressure to 20 mm. below auscultatory diastolic pressure. Changes in the volume pulse wave are transmitted to the recording system through a damped metallic diaphragm. The recording system is attached to a calibrated pipet in which a small droplet of 95 per cent ethyl alcohol moves freely with changes in displaced air volume. The movement of the alcohol droplet is recorded by focusing a beam of light on moving photographic paper in a camera container.

* Roniacol is a registered trademark of Hoffmann-La Roche, Inc., Nutley, New Jersey, and the material was kindly furnished by them.

The recording apparatus is used to measure absolute blood inflow volume in the finger by replacing the blood pressure cuff and diaphragm with a glass cylinder placed on the finger and sealed proximally with a rubber diaphragm, while the opposite end is attached by means of rubber tubing directly with the measuring pipet containing the alcohol droplet. Sudden venous occlusion at 60 mm. Hg pressure on the wrist converts the apparatus into a venous occlusion plethysmograph.

The flicker fusion thresholds were determined with the Krasno-Ivy Flicker Photometer.[5] Control levels of the flicker fusion threshold were obtained by seating the subject 5 feet from the flicker photometer in an evenly lighted room and while the subject concentrated on the flicker photometer light, reducing the flickering light from about 2900 flashes per minute until the subject reported "flicker." The procedure is repeated until approximately the same rate occurs three times consecutively. The same procedure is used after the administration of the test drugs.

Methods. Twelve normal white men, varying in age from 20 to 60 years, were used in all tests. For each determination the individuals were rested for 30 minutes before the control readings were taken. Room temperatures varied between 20 and 23 C. All the determinations were made with the subjects in the sitting position.

Each individual was tested twice with the placebos of lactose, and with 50, 100, and 200 mg. of Roniacol. Each test was done on a different day, but only twice weekly to prevent adaption to the drug. The drugs were prepared in identical tablets and taken orally. Oscillometric tracings from the right arm, pulse rates, and auscultatory blood pressures, were taken from each individual as controls, and repeated every 30 minutes for three hours after oral administration of the tablets.

The tests were repeated with identical drugs and doses, each again on different days, twice weekly. Oscillometric tracings were taken from the third finger right hand. Simultaneous flicker fusion thresholds were determined. Determinations of both were taken before the drugs were administered, and every 30 minutes thereafter for three hours.

The procedure was again repeated with the identical drugs and doses. Digital venous occlusion plethysmographic volume changes were recorded utilizing the Johnson Recording Oscillometer.

Results

General Effects of Roniacol

The symptomatic effects of Roniacol taken orally in the postabsorptive state are similar to those previously reported.[8] In this study the typical response began in anywhere from 5 to 30 minutes, although usually in 10 to 15

minutes, and lasted from 10 to 60 minutes. The onset usually began with a warm, prickling or tingling sensation, starting on the face and spreading to the forehead, ears, back of the neck, upper chest (especially anteriorly), usually progressing to the forearms and hands, occasionally to the legs and feet and rarely to the torso. Occasionally these sensations became burning and extremely unpleasant. A visible flush usually followed the onset of the symptomatic effects, but occasionally preceded or occurred simultaneously. The pattern of the flush was usually similar to the parethesia. The flush usually lasted longer than the parethesia.

Slight stomach ache, nausea, and headache occurred rarely. The extent of both the symptomatic effects and the visible flush were directly related to the dosage, usually none being present with 50 mg. Roniacol and almost always and to greater degrees with 200 mg. Roniacol.

Circulatory Effects of Roniacol

Results of all tests are summarized in table 1, and all statistical comparisons of significance in table 2.

(a) *Brachial Arterial Oscillometry.* After oral administration of 50, 100, and 200 mg. of Roniacol, there were no significant changes of the average blood flows for the test period of three hours when compared with the pre-Roniacol blood flow control values ($p > 0.5$), or when compared to the normal physiological variations after taking placebos ($p > 0.5$). The average rates of blood flow for the three-hour test period after oral administration of the placebo, 50, 100, and 200 mg. Roniacol are shown in figure 1.

There was no significant variation in the auscultatory systolic or diastolic pressures after oral administration of 50, 100, and 200 mg. Roniacol when measured 30 to 60 minutes after administration and when compared either with the placebo values, or with their own pre-Roniacol control blood pressure values

TABLE 1.—*Circulatory Effects of Roniacol**
For three-hour test period

	Placebo	Roniacol 50 mg.	Roniacol 100 mg.	Roniacol 200 mg.
Average Rate of Brachial Blood Flow†	1937.2 ± 93.2	1925.7 ± 84.3	1978.9 ± 74.2	1962.4 ± 64.0
Maximal Change of Brachial Blood Flow†	+250.1 ± 108.2	+142.6 ± 154.9	−15.2 ± 167.3	−24.9 ± 170.0
Average Rate of Digital Blood Flow†	200.2 ± 20.2	202.6 ± 17.7	189.7 ± 15.7	194.9 ± 25.9
Maximal Change of Digital Blood Flow†	−29.8 ± 29.7	−49.5 ± 29.3	+17.1 ± 23.3	−49.5 ± 36.6
Average Pulse Rate Per Minute	61.6 ± 2.4	60.4 ± 2.7	58.6 ± 2.4	61.2 ± 2.6
Maximal Change in Pulse Rate Per Minute	1.9 ± 3.0	0.8 ± 2.7	0.5 ± 2.9	4.2 ± 3.1
Average Systolic Pressure in mm. Hg	115.8 ± 9.5	115.1 ± 11.7	110.1 ± 8.0	113.7 ± 7.1
Average Diastolic Pressure in mg. Hg	69.6 ± 7.0	67.3 ± 7.6	66.0 ± 6.0	66.5 ± 7.2
Average Maximal Change in Systolic Pressure	−1.1 ± 1.8	−0.7 ± 1.8	1.5 ± 1.4	0.9 ± 1.2
Average Maximal Change in Diastolic Pressure	0.9 ± 1.9	0.9 ± .7	1.5 ± 1.6	1.3 ± 1.8
Average Digital Blood Flow by Venous Occlusion Plethysmography	3.6 ± 1.3	3.5 ± 1.6	3.7 ± 1.6	3.4 ± 1.8
Maximal Flicker Fusion Threshold Change	29.0 ± 11.4	26.7 ± 16.5	30.0 ± 33.2	28.3 ± 25.6

* All values represent averages of 12 normal male subjects.
† Measured in oscillometric units.

($p > 0.5$). The average systolic and diastolic blood pressures for the 12 subjects showed only slight average variation (fig. 2).

There was no significant difference between the normal physiologic variations in pulse rate with placebo and the pulse rates after oral administration of 50, 100, and 200 mg. Roniacol ($p > 0.5$). The average pulse rates for the 12 subjects showed very small average

TABLE 2.—*Statistical Significance of Comparison of Blood Flow Changes between Placebo and Various Doses of Roniacol*

	Comparison between Placebo and Roniacol Dose	No. Subjects	t	p
Digital arterial blood flow (maximal changes)	− 50 mg.	12	.61	0.5
	−100 mg.	12	1.07	0.3
	−200 mg.	12	.43	0.5
Digital arterial blood flow (average three-hour flow)	− 50 mg.	12	.13	0.5
	−100 mg.	12	.81	0.4
	−200 mg.	12	.26	0.5
Maximal change in pulse rate	− 50 mg.	12	.24	0.5
	−100 mg.	12	.32	0.5
	−200 mg.	12	.43	0.5
Systolic blood pressure changes	− 50 mg.	12	.14	0.5
	−100 mg.	12	.22	0.5
	−200 mg.	12	.62	0.5
Diastolic blood pressure changes	− 50 mg.	12	.005	0.5
	−100 mg.	12	.28	0.5
	−200 mg.	12	.64	0.5
Brachial arterial blood flow (maximal changes)	− 50 mg.	12	.71	0.4
	−100 mg.	12	1.10	0.2
	−200 mg.	12	1.20	0.2
Brachial arterial blood flow (average 3 hour flow)	− 50 mg.	12	.13	0.5
	−100 mg.	12	.43	0.5
	−200 mg.	12	.22	0.5
Digital venous occlusion plethysmographic blood flow changes	− 50 mg.	12	.43	0.5
	−100 mg.	12	.76	0.4
	−200 mg.	12	.94	0.3
Flicker fusion threshold changes	− 50 mg.	12	.19	0.5
	−100 mg.	12	.03	0.5
	−200 mg.	12	.03	0.5

variations during the three hours (fig. 3). The average maximal pulse rate change from the pre-Roniacol levels was 0.75 ± 2.7 beats per minute after 50 mg. Roniacol, 0.5 ± 2.9 beats per minute after 100 mg. Roniacol, and 4.2 ± 3.1 beats per minute after 200 mg. Roniacol, compared with the 1.9 ± 3.0 beats per minute after the placebo.

(b) *Digital Oscillometry.* Average blood flow values for the three-hour test period for the 12 subjects, in amplitude oscillometric units per minute, show no statistically significant

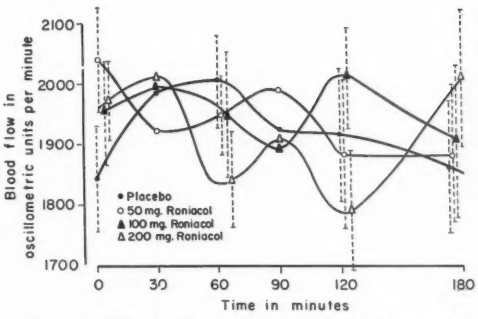


FIG. 1. Effects of Roniacol on brachial arterial blood flow. In all figures, individual points on the graph represent the average of 12 normal male subjects. The vertical lines represent the standard errors of the group means.

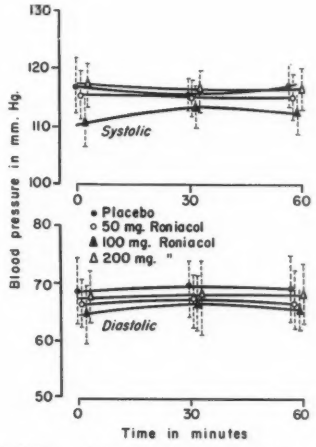


FIG. 2. Effect of Roniacol on auscultatory systolic and diastolic pressure. See also legend to figure 1.

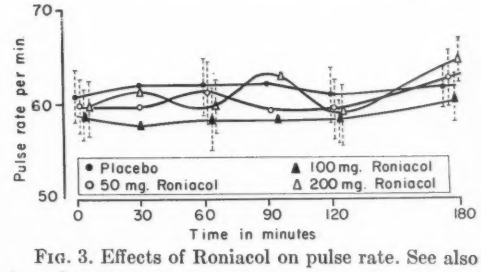


FIG. 3. Effects of Roniacol on pulse rate. See also legend to figure 1.

difference between the physiologic variation in placebo values during the three hours and the maximal individual fluctuations of the circulatory flow after oral administration of 50, 100, and 200 mg. of Roniacol ($p > 0.5$). The average rates of digital blood flow for the three-hour test period after administration of placebo, 50, 100, and 200 mg. Roniacol are shown in figure 4.

(c) *Digital Venous Occlusion Plethysmography.* There was no significant variation in the average blood flow for the three-hour duration of the test after 50, 100, and 200 mg. Roniacol when compared with the placebo values or the pre-Roniacol blood flow levels ($p > 0.5$).

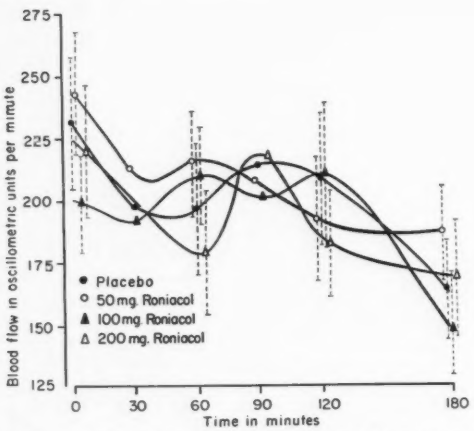


FIG. 4. Effects of Roniacol on digital blood flow. See also legend to figure 1.

(d) *Flicker Photometry.* There was no significant variation in the average maximal flicker fusion threshold change for the three-hour duration of the test after administration of 50, 100, and 200 mg. Roniacol, when compared to the pre-Roniacol control values or the placebo values ($p > 0.5$).

DISCUSSION

The rate of blood flow in the hand and foot is changed readily by vasoconstrictor stimuli, although the circulation in the forearm and leg is, for the most part, unaffected by stimuli which do not have a cardiovascular effect and enhanced by those which appear to increase cardiac output.[12] As Roniacol produces no significant change in blood pressure, pulse rate or the systolic ejection expansion of the brachial artery, it consequently appears to have no significant effect on cardiac output.

Roniacol has no significant effect on digital blood flow as measured both in oscillometric units, and directly by venous occlusion plethysmography.

As the volume pulse is a sensitive indicator of the vasomotor activity which is of insufficient degree to show itself on blood pressure changes,[1] lack of significant alteration of the volume pulse following oral administration of 50, 100, and 200 mg. of Roniacol indicates that it has no significant effect on the sympathetic vasomotor tone in the upper extremity. As the lower extremity normally has even a higher degree of sympathetic tone than the upper extremity[1] even less effect would be expected on the lower extremity.

The lack of significant change of the flicker fusion threshold indicates that Roniacol has no significant vascular effects on the visual apparatus. With vasodilation there would have been marked depression of the threshold.

It is unlikely that any significant transient effects occurred between determinations, as most of the 30-minute determinations were made during the period of both maximal symptoms and visual flush.

The presence of flush without measurable changes in circulation, as determined by the tests employed in this study, probably indicates that the clinical effects of Roniacol are due to dilatation of the skin capillaries. This might account for some of the favorable results reported with chronic trench foot[6] and with gangrenous skin.[7] The failure to demonstrate circulatory changes despite the visible flush may be due to several factors, such as (1) insufficient sensitivity of the tests for recording the effects of flushing, or (2) concomitant vasoconstriction in other vessels in the same limb, thus producing no change in the total blood flow. These studies were performed using single doses of Roniacol on normal men and do not necessarily indicate the action of the drug when given continuously in the treatment of disease.

Summary and Conclusions

Orally administered Roniacol in single doses up to 200 mg. has no significant effect on the auscultatory blood pressure, pulse rate, or circulation of *normal* individuals as measured by: (1) brachial arterial and digital oscillometry, (2) digital venous occlusion plethysmography, and (3) flicker photometry.

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The Atrial Border Electrokymogram in Mitral Regurgitation

By Louis A. Soloff, M.D., Jacob Zatuchni, M.D., M.S. (Med.), and Herbert M. Stauffer, M.D., M.S. (Rad.)

Border electrokymograms of the cardiovascular silhouette in various views were obtained at approximately 1.0 cm. intervals in 28 subjects to determine the constancy and the specificity of the atrial border motion and to determine its ability to differentiate organic from functional apical systolic murmurs. Although a "plateau" curve previously reported as pathognomonic of organic mitral regurgitation was obtained in 12 of the 13 individuals with various types of heart disease and with an apical systolic murmur, identical "plateau" curves were obtained in 10 of the 15 individuals with normal hearts and with no apical systolic murmur. Atrial curves previously reported as normal were also obtained in each of the 28 subjects studied. Some of the reasons for these results, which are at variance with those reported by others, are discussed.

THE CLINICAL significance of an apical systolic murmur may not be apparent even after the most thorough studies by conventional methods. Recently, it has been suggested that electrokymographic recordings of atrial border motion in individuals with organic mitral regurgitation are pathognomonic and differ significantly from those of subjects with physiologic mitral systolic murmurs.[3, 4] The atrial electrokymogram in the individual with organic mitral regurgitation is said to show a curve characterized by a positive "plateau" during ventricular systole due to a sustained outward movement of the left atrial border, beginning with the initial vibrations of the first heart sound and terminating soon after the second heart sound.[3, 4] Such an objective finding, if present, is obviously of extreme importance.

The purpose of this report is to present our findings in 15 individuals with normal hearts and 13 with various types of heart disease in an effort to determine the constancy and the specificity of the atrial border electrokymogram in those with organic mitral regurgitation and in those without it.

Methods and Material

The improved electrokymograph described by Henny, Boone and Chamberlain[2] was used to record the cardiovascular border movements. The subject was in the sitting position and electrokymograms were obtained of the borders of the cardiovascular silhouette at approximately 1.0 cm. intervals, in the posteroanterior, left oblique and right oblique anterior views. The position of the pickup device was noted on an outline of the cardiovascular silhouette drawn on transparent paper superimposed upon the fluoroscopic screen. An average of 25 tracings was recorded for each subject. The exposure time varied from 14 to 22 minutes (10 roentgens per minute). The carotid pulse and heart sounds were recorded simultaneously for correlation of the electrokymogram with the mechanical cardiac cycle.

Twenty-eight subjects were studied. Of these, an apical systolic murmur was present in 13. Ten of the 13 had rheumatic mitral insufficiency, one chronic constrictive pericarditis, one Ebstein's anomaly and hypertension, and one a pulmonary artery aneurysm. Fifteen of the 28 subjects had no murmurs, including one with hypertension, two with sickle cell anemia, one with a gastric ulcer, and 11 normal male medical students. A summary of the clinical data may be found in table 1.

Results

Only the electrokymograms of the atrial borders will be discussed in detail in this study. Curves reported by others to be characteristic of atrial border motion in individuals with normal hearts are recorded as N (or "normal") in table 1; and, those having a "plateau" configuration, reported by others to be characteristic of atrial borders in individuals with organic mitral regurgitation, are recorded as P (or "plateau"). If the electrokymogram did

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not reveal either a "normal" or "plateau" atrial border motion, it was recorded as a question mark (?) in table 1, for then it was either not typical of any recognized border motion or was suggestive of an arterial or ventricular one, even though the fluoroscopist thought that the pickup device was over the atrial border.

The location refers to the region of the atrium in a specific positioning of the thoracic cage. Attempts to determine these regions more specifically were defeated by the variable results obtained even in the same tracing. Slight changes in positioning of the patient with respect to the fluoroscopic screen may also be responsible for the variability of the tracings.

In 12 of the 13 subjects with an apical systolic murmur, a typical "plateau" curve was obtained in either or both oblique views and occasionally over the left third segment or

TABLE 1.—*Summary of Clinical Data and Electrokymographic Results*

Subject	Diagnosis	Apical Systolic Murmur	Atrial Border Electrokymogram Position			
			Right Oblique Anterior	Left Oblique Anterior	P-A (left border)	P-A (right border)
1. J. A.	Rheumatic aortic and mitral stenosis and insufficiency.	Present	N & P	?	?	?
2. A. K.	Rheumatic aortic and mitral stenosis and insufficiency.	Present	P	N	?	?
3. R. N.	Rheumatic mitral insufficiency.	Present	N	N & P	N & P	?
4. E. D.	Rheumatic mitral stenosis and insufficiency.	Present	P	N	?	?
5. A. D.	Rheumatic mitral stenosis and insufficiency and interatrial septal defect.	Present	?	N & P	?	?
6. M. K.	Rheumatic aortic insufficiency and mitral stenosis and insufficiency.	Present	P	P	N	?
7. O. L.	Rheumatic mitral stenosis and insufficiency.	Present	N & P	P	?	?
8. S. L.	Rheumatic mitral stenosis and insufficiency.	Present	N & P	N & P	?	?
9. S. B.	Rheumatic mitral insufficiency and left atrial aneurysm.	Present	P	?	N	N & P
10. J. R.	Rheumatic mitral insufficiency.	Present	?	N & P	N	?
11. J. S.	Chronic constrictive pericarditis.	Present	?	?	N	?
12. A. H.	Ebstein's anomaly and hypertension.	Present	N & P	?	?	P
13. A. C.	Pulmonary artery aneurysm.	Present	N & P	?	?	?
14. J. W.	Sickle cell anemia. Normal heart.	None	N	?	?	?
15. D. F.	Sickle cell anemia. Normal heart.	None	N	N & P	?	?
16. U. D.	Hypertension. Cardiac examination neg.	None	P	N & P	?	?
17. L. C.	Gastric ulcer. Normal heart.	None	N & P	N	N	?
18. R. S.	Normal.	None	?	N	?	?
19. W. W.	Normal.	None	?	?	N	?
20. E. C.	Normal.	None	?	P	N	?
21. J. P.	Normal.	None	N & P	?	?	?
22. J. R.	Normal.	None	N & P	N & P	?	?
23. P. C.	Normal.	None	N	N	?	?
24. W. R.	Normal.	None	?	N & P	N	N
25. N. Y.	Normal.	None	?	N	N	N
26. H. W.	Normal.	None	P	N & P	?	?
27. J. A.	Normal.	None	?	P	N	?
28. R. S.	Normal.	None	P	N	?	?

(N—typical normal curve, P—typical plateau curve, ?—questionable curve).

If the electrokymogram did not reveal either a "normal" or "plateau" atrial border motion, it was recorded as a question mark (?), for it was then either not typical of any recognized border motion or suggestive of an arterial or ventricular one, even though the fluoroscopist thought that the pickup device was over the atrial border.

over the right border of the heart in the postero-anterior view. Typical electrokymograms are shown in figure 1, tracings *J* and *L*. The tracing made from a patient with constrictive pericarditis, who had an apical systolic murmur, did not have a "pleatau" curve. But normal atrial curves were also obtained in all of these patients, even at times in the same view in

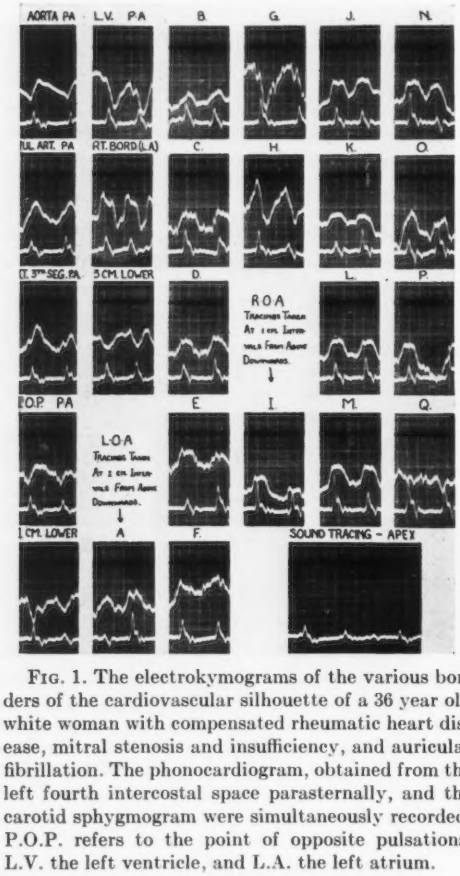


FIG. 1. The electrokymograms of the various borders of the cardiovascular silhouette of a 36 year old white woman with compensated rheumatic heart disease, mitral stenosis and insufficiency, and auricular fibrillation. The phonocardiogram, obtained from the left fourth intercostal space parasternally, and the carotid sphygmogram were simultaneously recorded. P.O.P. refers to the point of opposite pulsations, L.V. the left ventricle, and L.A. the left atrium.

which abnormal curves were previously or subsequently recorded.

Furthermore, typical "plateau" curves were obtained in seven normal male medical students and in three hospitalized patients with normal hearts, none of whom had an apical systolic murmur. A typical example of this is shown in figure 2, tracing *A*.

A summary of these findings is given in table 1.

DISCUSSION

The normal atrial electrokymogram is didactically described as being composed of three waves, one occurring in atrial systole and two in atrial diastole.[3, 4] The first, a downward curve, is interpreted as being due to inward movement of the contracting atrium. This wave

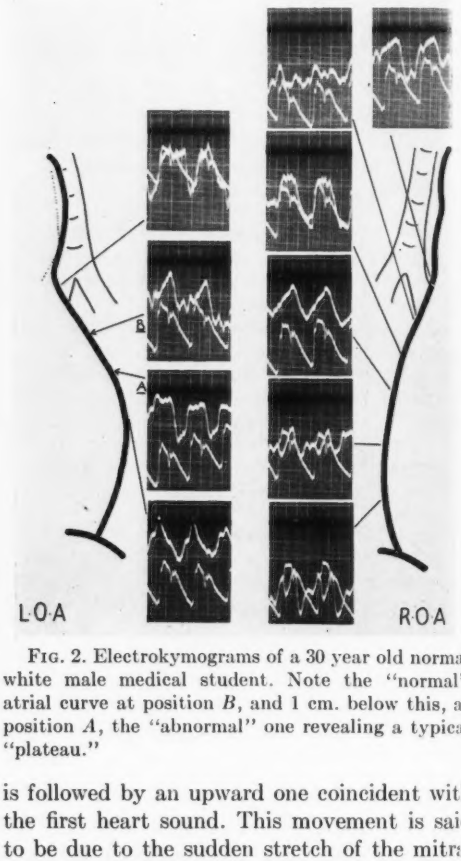


FIG. 2. Electrokymograms of a 30 year old normal white male medical student. Note the "normal" atrial curve at position *B*, and 1 cm. below this, at position *A*, the "abnormal" one revealing a typical "plateau."

is followed by an upward one coincident with the first heart sound. This movement is said to be due to the sudden stretch of the mitral valve at the beginning of the isometric contraction of the ventricle.[4] The succeeding downward curve is believed to represent movement of the atrioventricular septum and attached atria toward the apex. A gradual upward movement, presumably due to gradual filling of the atria, is then recorded. It continues until shortly after the second heart sound. The curve then de-

clines slowly presumably due to atrial emptying and terminates in the sharp downward movement thought to represent atrial contraction[4] (figure 2, tracing *B*).

The duration of the "presystolic" inward movement recorded over the atria varied from one individual to another and even in the same individual from one time to another. The time varied from 0.04 to 0.16 second compared with the average electrical atrial contraction of 0.11 second for a cardiac cycle length of 0.80 second.[5] This "presystolic" movement was present in two individuals with auricular fibrillation, a rhythm that is said to abolish this type of motion.[3] The electrokymograms of one of these patients is shown in figure 1.

There was no correlation between the magnitude of the upward movement coincident with the first heart sound and the amplitude of the carotid sphygmogram (fig. 1, tracing *O*). This lack of correlation appears to contradict the accuracy of the assumption that this movement is related to the force of systolic contraction.[4]

The prediction that a "plateau" curve would appear in mitral regurgitation was based upon known clinical and experimental physiologic studies in man and in animals with mitral regurgitation. Mitral regurgitation is expected to occur in incompetency of the mitral valve because intraventricular pressure exceeds that of intra-atrial pressure during the phases of isometric contraction, ejection, protodiastole, and isometric relaxation.[5] It appears likely that maximal regurgitation will occur during the phase of systolic ejection, when the intraventricular–intra-atrial pressure difference is greatest. Volume curves in experimental mitral regurgitation actually do show that the greatest increase in left atrial volume occurs when the blood is entering the aorta whereas only a small increase occurs during isometric contraction.[5]

This type of upward movement during systolic ejection was recorded by Chamberlain and Dock with Ruggles' cinematograph.[3] Similar curves recorded electrokymographically are shown in figures 3*A* and 3*B*. These curves were obtained from a 13 year old girl with inactive rheumatic mitral insufficiency and slight left ventricular enlargement. Over the left atrium, an accentuated upward movement occurs coincident with the first heart sound. A downward movement follows quickly. With systolic ejection as determined by the carotid sphygmogram (corrected by 0.01 second for the lag in the air-conduction system), an upward movement begins. It rises at first rapidly and then continues a slower ascent until the peak is reached shortly after the second heart sound.

It was therefore greatly disappointing to us that in this small group, typical "plateau" curves were derived not only from individuals with organic mitral regurgitation but also from many with normal hearts. It may be true that with isolated tracings, "plateau" curves are more commonly derived from those with regurgitation than from those with normal hearts, but with multiple explorations many "plateau" curves from individuals with normal hearts will be uncovered. A statistical analysis of limited electrokymographic exploration of left atrial border movements appears to us to be without meaning.

There are many possible explanations for our results being at variance with those of others. Some of these explanations are applicable to the problem of electrokymographic border motions in general.

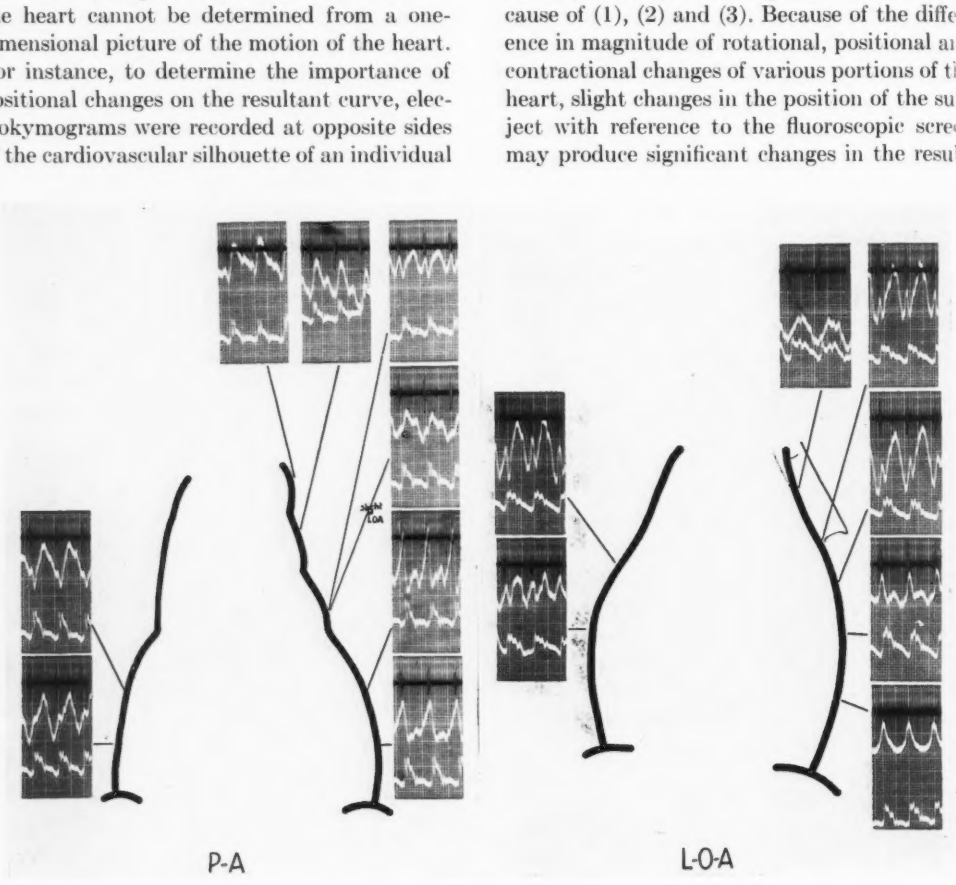
1. *Difficulty in reading records.* The records were studied as carefully as one possibly could. This criticism that appears picayune must always be raised, for electrokymograms are difficult to read because of the frequency of minor deviations in succeeding complexes.

2. *Inaccurate localization of the left atrium.* All fluoroscopic localizations were made by one of us (H.M.S.). We should like to emphasize that the atrium is not easy to identify in its entirety especially when it is not enlarged.

3. *Misinterpretation of positional changes.* Any movement of the ventricles produces a shift in the position of the atria because the two are intimately attached to each other. Furthermore, the heart is an irregular three-dimensional object that has complex simultaneous motions composed of (a) change in position as a whole, (b) contraction or relaxation and (c) rotation. All of these motions are transmitted to some extent to the atria, which in turn are undergoing their own independent

complex motions. The individual contributions of rotation, displacement and contraction of the heart cannot be determined from a one-dimensional picture of the motion of the heart. For instance, to determine the importance of positional changes on the resultant curve, electrokymograms were recorded at opposite sides of the cardiovascular silhouette of an individual with an aneurysm of the pulmonary artery proved by angiocardiography. These curves, illustrated in figure 4, indicate that an outward motion recorded on one side is accompanied by a simultaneous inward movement on the other side, regardless of the underlying anatomic structure. Perhaps simultaneous recordings of this sort may help to differentiate positional outward movements from true "plateau" movements.

4. *Changing position of the patient.* This factor may actually be an important contributing cause of (1), (2) and (3). Because of the difference in magnitude of rotational, positional and contractional changes of various portions of the heart, slight changes in the position of the subject with reference to the fluoroscopic screen may produce significant changes in the resultant motion recorded by the electrokymogram.



A *B*

FIG. 3. The electrokymograms of the cardiovascular borders in *A*, the posteroanterior view, and *B*, the left anterior oblique view obtained in a 13 year old white girl with inactive, compensated, rheumatic heart disease with mitral insufficiency and slight left ventricular enlargement.

5. *Inability of the photoelectric cell to discriminate anatomic causes for changes in light intensity.* Too often it is said that the photoelectric cell is more sensitive to changes in light intensity than the human eye and is therefore superior in detecting motion which is translated into changes in light intensity. The photoelectric cell is more sensitive than the

human eye to a change in light intensity but is less sensitive in its discrimination of the components contributing to the changing light intensity. The human eye sees the atrium moving; the photoelectric cell cannot register the change in light intensity produced by the movement of the atrium without including all changes in light intensity produced by movements of all structures beneath the photoelectric cell through the entire thickness of the

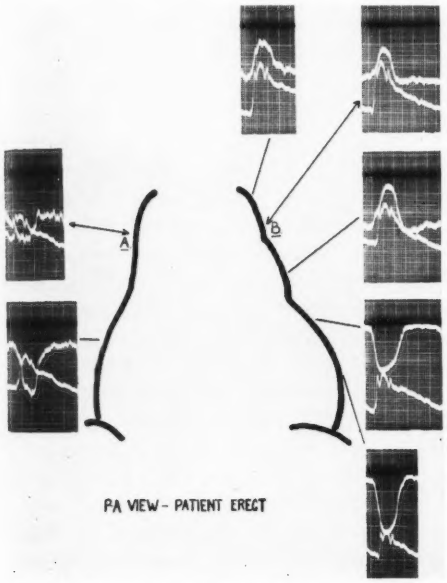


FIG. 4. Electrokymograms of the cardiovascular borders (posteroanterior view) in a patient with a pulmonary artery aneurysm. Note the inward movement recorded at *A* and the outward movement recorded at *B* even though both were motions of the great vessels.

chest wall. There are important structures anterior and posterior to the atrium depending upon the position of the chest wall with reference to the fluoroscopic screen which may contribute largely to changes in light intensity either in the same direction or in opposite direction to the change produced by the atrium. For instance, the atrium may partly overlap a pulmonary artery, or the aorta, or even a portion of the ventricle depending upon the relationship of the thoracic cage to the photoelectric cell. A great vessel or ventricular curve may then be superimposed upon the atrial curve and if large enough could produce a distortion sufficient to give rise to a "plateau" curve.

For all these reasons, there is no such thing as an atrial border electrokymogram in the purest sense and interpretations of individual features of the curve derived as a single perpendicular motion is extremely difficult or impossible. Perhaps multiple simultaneous border electrokymograms or some type of quantitative electrokymogram may permit interpretations. Notwithstanding these inherent difficulties, it is also possible that an empiric analysis of a large number of electrokymograms may define those curves that do not occur in the normal.

SUMMARY AND CONCLUSIONS

1. Border movements of the cardiovascular silhouette in various views were recorded electrokymographically at approximately 1.0 cm. intervals in 28 subjects. The atrial border electrokymogram is discussed in detail in this study.

2. In 12 of 13 subjects with an apical systolic murmur, a typical "plateau" curve, reported by others to be characteristic of left atrial border motion in organic mitral regurgitation, was obtained in either or both oblique views and occasionally in the posteroanterior view over the left third segment or over the right border of the heart.

3. Identical "plateau" curves were obtained from the atrial borders of 10 subjects with normal hearts, including seven normal male medical students and three hospitalized individuals with no apical systolic murmur.

4. Curves said to be characteristic of atrial border motion in subjects with normal hearts were also recorded at various positions in each of the 28 subjects studied.

5. A "plateau" curve was more frequently obtained in those with organic mitral regurgitation.

6. Some explanations for these results are discussed.

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Effect of Cholesterol Feeding during Pregnancy on Blood Cholesterol Levels and Placental Vascular Lesions

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After establishing the normal variations in blood cholesterol levels on a recorded dietary regimen during pregnancy, 2 Gm. of cholesterol in chocolate candy were fed daily without significant alteration in blood cholesterol levels or placental vascular lesions.

THE RECENT clamor regarding the role of dietary cholesterol in the production of human atherosclerosis occasioned this study. Since this work has been in progress, several studies[1–3] have indicated that normal variations in cholesterol intake have little or no effect on blood cholesterol levels. A recent report[2] indicates that unless very sharp restriction of cholesterol intake (less than 200 mg. per day) is obtained, a drop in blood cholesterol levels will not occur. Older reports[4–6] however, have indicated that with an increase in cholesterol intake hypercholesterolemia of at least some degree will occur. Dock[7] particularly emphasized the importance of dietary cholesterol on the development of atherosclerosis.

This study was undertaken to determine the effect of a sharp increase in dietary cholesterol intake on blood cholesterol levels in young pregnant women. Inasmuch as there is normally a rise in serum cholesterol during pregnancy it was thought that feeding additional cholesterol during this period might produce an exaggerated response in serum cholesterol levels.

Methods and Procedures

Young pregnant women resident in a maternity home and hospital from the fifth month of pregnancy to term were used as subjects. All of these individuals were healthy and were selected to eliminate any complication of pregnancy.

The nutritionist member of this group (E. L.) trained all the girls in this study in the technic of recording their food intake. Although the basic diet was not rigidly controlled, and indeed was not an optimum diet for pregnancy, all food eaten by these subjects during the time they were resident in this institution was carefully recorded. During the course of the pregnancy total serum cholesterol, cholesterol esters and serum lipid phosphorus values were obtained monthly using a modification of the Schoenheimer-Sperry technic.[8] In addition all of these patients had the usual antepartum monthly routine examinations. Thirty-five subjects were followed through pregnancy on the usual hospital diet. A second group of 30 subjects received 2 Gm. of cholesterol daily prepared in various types of fancy chocolate candies in addition to the usual hospital diet.

At the time of delivery the intact placentas were placed in formalin and after three months fixation the placentas were weighed and serially sectioned at distances of approximately 1 cm. for evidences of vascular lesions. At the same time the structures of the umbilical cord were laid open for detection of vascular lesions.

Results

Table 1 records the average age and the weight changes in both the normally fed and cholesterol-fed group. Table 2 records the dietary intake of protein and fat and the total caloric intake per day during a representative week of the dietary recording. The data presented in this table do not represent an accurate average of the intake during the entire period of observation but rather an average of the dietary intake during a representative week during the period of observation. It

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should be noted that both the caloric and fat intake of the cholesterol-fed group were slightly lower than the intake for the normally fed subjects.

TABLE 1.—*Average Age and Weight Changes.*

	Normal Diet	Cholesterol Fed
Average Age	21.8 yrs.	19.9 yrs.
Average Initial Wt.	117 lb.	122 lb.
Average Term Wt.	144 lb.	146 lb.
Average Gain Wt.	27 lb.	24 lb.
Average Fetus Wt.	7 lb. 0 oz.	6 lb. 13 oz.

TABLE 2.—*Caloric Intake and Dietary Intake of Protein and Fat*

	Normal Diet	Cholesterol Fed
Protein	68 Gm.	72 Gm.
Fat	78 Gm.	56 Gm.
Calories	2000	1800

mally fed group, this is not statistically significant.

Examination of the placentas failed to reveal any evidence of any difference in vascular structure, in occurrence of gross infarcts, or in the development of placental vascular lesions between the normally fed and the cholesterol-fed group.

DISCUSSION

Although the cholesterol intake of the normally fed group receiving 78 Gm. of fat per day was not accurately determined it can be estimated that this was a relatively normal and perhaps even a low cholesterol intake. The addition of 2 Gm. of cholesterol per day certainly should provide a tremendous overload of dietary cholesterol. It is regretted that the cholesterol-fed group did not receive an exactly similar intake of fat during the period of observation, as this may be in part responsible for the observation of the slight lower cholesterol levels in the cholesterol-fed group. Probably this is also responsible for the slightly smaller weight gain of the group receiving cholesterol. However, it is quite obvious that a significant increase did not occur in any of the lipid fractions studied during the period of cholesterol feeding.

TABLE 3.—*Changes in the Lipid Fractions.*

	Total Serum Cholesterol mg./100 ml.				Serum Cholesterol Esters mg./100 ml.				Lipid Phosphorus mg./100 ml.				Cholesterol-Lipid Phosphorus Ratio			
	Normal Diet		Cholesterol Diet		Normal Diet		Cholesterol Diet		Normal Diet		Cholesterol Diet		Normal Diet		Cholesterol Diet	
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
5 mo.	235	±42	202	±29	171	±33	145	±15	12.1	±0.1	11.4	±1.5	18.0	±2.6	16.4	±3.2
No. cases	15		7		15		7		15		7		15		7	
6 mo.	227	±46	214	±36	162	±37	148	±24	13.1	±2.3	11.6	±1.6	17.6	±4.2	18.4	±2.9
No. cases	28		14		28		13		28		12		28		12	
7 mo.	240	±51	192	±33	167	±38	136	±24	13.0	±1.9	11.1	±1.8	18.1	±3.0	18.1	±3.4
No. cases	36		20		36		19		37		21		35		20	
8 mo.	250	±17	224	±11	178	±16	158	±9	13.7	±1.9	12.0	±2.3	18.4	±3.0	19.0	±3.3
No. cases	36		26		36		26		36		26		36		26	
9 mo.	257	±45	223	±26	177	±38	154	±24	14.5	±2.2	12.5	±2.2	18.2	±2.2	18.3	±3.7
No. cases	34		18		34		16		34		18		34		18	
Postpartum	244	±37	227	±37	170	±30	134	±21	13.6	±1.8	12.7	±1.8	18.1	±2.2	18.1	±0.8
No. cases	37		2		27		1		27		2		27		2	

The details of the changes in total serum cholesterol, cholesterol esters, lipid phosphorus, and the cholesterol–lipid phosphorus ratio are recorded in table 3 and the mean values in figure 1. These data indicate that feeding relatively large amounts of cholesterol failed to produce any demonstrable increase in any of these serum fractions. Although casual inspection of the graphs indicates that the values in the cholesterol-fed group were consistently lower than the values in the nor-

SUMMARY

The changes in total serum cholesterol, cholesterol esters, lipid phosphorus, and choles-

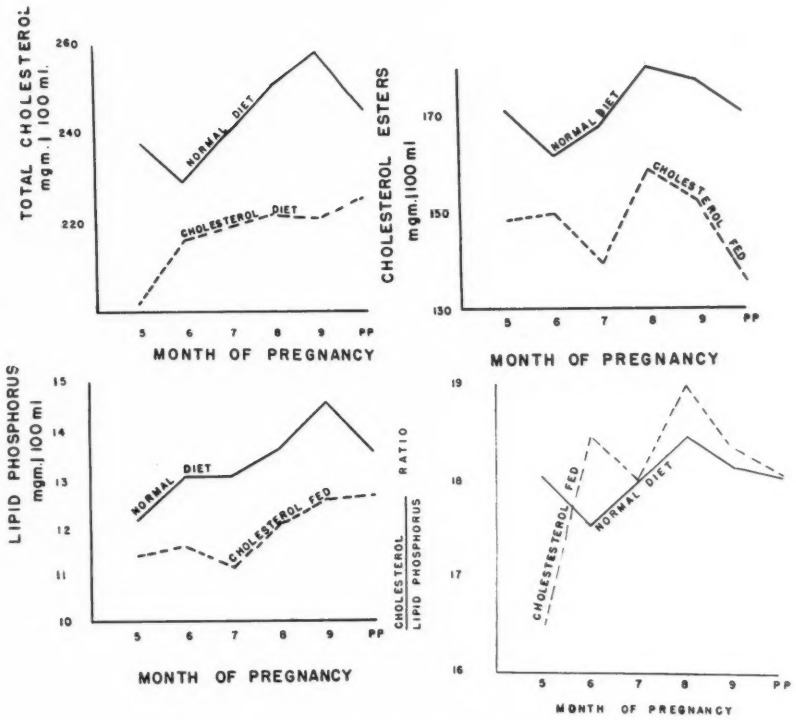

FIG. 1. Average values of lipid fractions in the last half of pregnancy.

terol–lipid phosphorus ratios were followed from the fifth month of pregnancy in 35 young women receiving a normal institutional diet and in 30 women receiving the same diet plus 2 Gm. of cholesterol daily supplied in fancy chocolate candy. No discernible rise in any of these lipid fractions occurred in the cholesterol-fed group over those noted in the normally fed group.

From these data it is evident that from the fifth month of pregnancy, on the addition of a large amount of dietary cholesterol fails to produce any increase in serum cholesterol levels or in vascular lesions of the placenta.

It is felt that this evidence indicates the fallacy of attributing changes in serum cholesterol levels to moderate changes in the dietary intake of cholesterol.

ACKNOWLEDGMENT

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The Use of an Oximetrically Determined Circulation Time from the Right Ventricle to the Ear in Congenital Heart Disease

By Richard P. Lasser, M.D., Alvin J. Gordon, M.D., Raymond Borun, M.D., and Frederick H. King, M.D.

Evans Blue (T-1824) was injected into the right ventricle through a cardiac catheter and the time of the arrival of dye at the ear was measured with an oximeter. This circulation time appeared to indicate reliably the presence of venoarterial shunting through an over-riding aorta. The difficulties ordinarily encountered in positive identification of this defect are discussed. The importance of the identification, particularly with regard to the differential diagnosis between tetralogy of Fallot and pulmonary stenosis with an interatrial communication, is stressed.

THE TIME interval between the injection of dye into the right ventricle and its detection in the capillaries of the ear by an oximeter was measured in 18 individuals during the course of cardiac catheterization. This test of circulation time was designed as a supplement to the cardiac catheterization of patients with congenital heart disease in order to assist in the identification of over-riding aorta. It was anticipated that the short circuit of the lung and left heart circulation which resulted from the venoarterial shunting would be detectable as a shortened "circulation time."

In all previous investigations of the circulation time in congenital heart disease,[1–4] the test substance was injected into a peripheral vein. Using such a technic, abnormally rapid arrival of the test substance at the point of detection was frequently demonstrated. However, there was equally frequent failure to demonstrate shunts in patients who had marked arterial unsaturation. Moller, for example, in a study using fluorescein, reported that a shortened dye arrival time was observed in only 7 of 18 patients with tetralogy of Fallot. Moreover, the problem of the localization of the site of the shunt, which is the chief diagnostic concern, is not solved even by the finding of a rapid arrival time. This same difficulty applies to all technics in which substances are injected into a peripheral vein, angiocardiography included. Rapid visualization of the aorta, even if simultaneous with that of the pulmonary artery, cannot be considered positive proof of over-riding of the aorta, as will be subsequently demonstrated.

The importance of a clear distinction between cases of venoarterial shunt due to defective interatrial septum accompanied by pulmonic stenosis and those due to tetralogy of Fallot lies in the fact that the operative procedure of choice at present is valvulotomy in the former and the Blalock-Taussig procedure in the latter.[5] This consideration was the reason for the selection of the right ventricle as the site of release of the dye.

Technic

The 18 subjects in whom the test was performed were, with one exception, patients suspected or known to have congenital heart disease. The sole exception was an adult with normal cardiovascular dynamics who was catheterized as part of a study of cardiac output and renal function.

The earpiece of a Millikan-type oximeter was fastened to the patient's ear at the time when the cardiac catheter (No. 6F or 7F) lay in the right ventricle at the tricuspid orifice. The location of the catheter was always confirmed by fluoroscopy and pressure tracings. When the ear was sufficiently warmed to insure adequate vasodilation, rapid injection of a 0.5 per cent aqueous solution of Evans Blue (T-1824) was made through the catheter. Three cc. of dye were used in children and 5 in adults. A stopwatch was started at the beginning

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of injection and was stopped at the first perceptible deflection of the oximeter galvanometer. The total time consumed was taken as the circulation time. This included the time for passage of the dye through the catheter which was estimated by tests outside the body to be about 0.75 to 1.0 second. The procedure was simple to perform, did not interfere with the progress of the catheterization, and gave sharp endpoints.

The relation between the initial galvanometric deflection and the appearance of dye as determined by an arterial concentration curve is not known. Therefore, the values recorded probably do not represent the true minimum circulation time. They merely represent the apparent minimum dye appearance time which is dependent upon the sensitivity and speed of response of the detecting instrument used. Since the instrument was always the same, values within this series are comparable but comparisons with values obtained with other instruments or technics would be hazardous.

Results

The purpose of the study was to determine whether a reliable abbreviation of the circulation time could be detected in patients believed to have an over-riding aorta. The results are therefore arranged in order of increasing circulation time (table 1). The table also shows the age, heart rate during the catheterization, arterial oxygen concentration and the clinical diagnosis.

The first five cases all show circulation times under 5 seconds, the average of the five being 4.0 seconds. All of these children were cyanotic. Four of the five were thought to have tetralogy of Fallot. This diagnosis was based upon the clinical findings, cardiac fluoroscopy, angiocardiographic appearance and the data obtained by cardiac catheterization. As indicated previously, direct and positive proof of overriding aorta is lacking because in no case did the catheter enter the aorta from the right ventricle, and no child has died and come to postmortem examination. One child (A. M., case 3) was operated upon by Drs. Gabriel Seley and Arthur S. W. Touroff who performed a Blalock-Taussig anastomosis, with marked clinical improvement. The fifth child of this

Table 1.—*Summary of Eighteen Cases in Which Right Ventricle to Ear Circulation Time was Determined*

Case No.	Name	Age	Heart Rate	Arterial Oxygen Saturation	Circulation Time	Diagnosis:
				(%)	(sec.)	
1	J. G.	5	96	70	3.5	Eisenmenger's complex with interatrial septal defect
2	G. L.	6	120	82.5	3.5	Tetralogy of Fallot
3	A. M.	2½	120	77.6	4.0	Tetralogy of Fallot with interatrial septal defect and right aortic arch
4	S. B.	8½	90	89	4.4	Tetralogy of Fallot
5	M. D.	3½	110	visibly cyanotic	4.7	Tetralogy of Fallot
6	C. R.	3	110	87.3	5.3	Lutembacher's syndrome
7	S. L.	19	90		5.5	Isolated pulmonary stenosis
8	C. B.	11	90	96.3	6.0	Patent ductus arteriosus
9	M. D.	32	100	59.8	6.0	Pulmonary stenosis with interatrial septal defect
10	G. K.	13	105	97.0	6.2	Normal with prominent pulmonary artery
11	R. P.	12	90	100	7	Normal with prominent pulmonary artery
12	M. A.	11	115	95.7	7	Pulmonary stenosis with interatrial septal defect
13	M. H.	8	80	93.4	7	Subaortic stenosis
14	S. D.	6	85	98.4	9	Isolated pulmonary stenosis
15	E. G.	6½	100	93	9	Patent ductus arteriosus
16	L. G.	19	70	92.6	9.5	Isolated pulmonary stenosis
17	V. D.	30	80	99	9.5	Pulmonary stenosis with interatrial septal defect
18	E. W.	40	70	no cyanosis	10	Normal

group furnished indirect proof of over-riding aorta. The catheter, in this patient, passed through an atrial septal defect into the left atrium and left ventricle. The oxygen saturation of blood in the left ventricle was 90.8 per cent while that of the femoral artery was 70.4 per cent, demonstrating that a large veno-arterial shunt existed which was distal to the left ventricle, that is, an over-riding aorta. (J. G., case 1).[9]

None of the remaining 13 patients was believed to have over-riding of the aorta. This belief was based on the clinical findings, the angiocardiographic visualization of the heart and on the absence of arterial unsaturation or visible cyanosis in 11 of the 13. Of the two patients in whom arterial unsaturation was found, one came to postmortem examination (M. D., case 9) and will be discussed later. The other (C. R., case 6) was a child with Lutembacher's syndrome whose heart was large with a large pulsatile pulmonary artery and increased vascular markings. Catheterization disclosed the presence of an atrial septal defect and normal pressures within the right ventricle and pulmonary artery. Over-riding of the aorta was excluded, therefore, because of the absence of hypertension within the right ventricle.[6]

The patient who came to postmortem examination was one who presented the very problem in differential diagnosis which is at the basis of this study. Cardiac catheterization showed the presence of an atrial septal defect, pulmonary stenosis and marked elevation of pressure within the right ventricle. Arterial unsaturation was present. Angiocardiographic study, performed by Dr. Sigmund A. Brahms, demonstrated the presence of Diodrast within all chambers of the heart, the pulmonary artery and aorta within 1.2 seconds after injection. The consensus was that the amount of Diodrast present in the aorta was greater than could be accounted for by the opacity of the left atrium and ventricle. Therefore it was believed that an over-riding aorta did exist. The patient died some time later and postmortem examination revealed the presence of an atrial septal defect and marked valvular pulmonary stenosis. The interventricular septum was closed and no over-riding of the aorta could be demonstrated.

It was deemed probable that no over-riding aorta existed in any member of this group in which the circulation time was greater than 5 seconds. The values ranged from 5.3 to 10 seconds with an average of 7.4 seconds. The average circulation time of this random group of patients who probably did not have over-riding aorta was then 1.8 times as long as the average of the group with over-riding aorta. Moreover, there was no overlap between the shortest time of this patient group (5.3 seconds) and the longest time of the initial group (4.7 seconds).

TABLE 2.—*Comparison of Three Patients with Over-riding Aorta (Group I) with Three Children of Similar Ages without This Anomaly (Group II)*

Age				Circulation Time		Heart Rate	
I		II		I	II	I	II
J.G.	5	S.D.	6	3.5	9	96	85
G.L.	6	E.G.	6½	3.5	9	120	100
S.B.	8½	M.H.	8	4.4	7	90	80
Average.....	6.5		6.8	3.8	8.3	102	88

The patients in this latter group however, were, on the average, much older than those in the initial group. This fact raised some question about whether the two groups were really comparable and therefore whether the observed difference of circulation time was attributable to venoarterial shunting or merely to the difference in age. To eliminate the age factor, table 2 was drawn up comparing three children of similar ages in both groups. The disparity between the average of the circulation times was even more marked than that observed when both entire groups were compared.

There is one further factor to be considered and that is the influence of heart rate. The average rate in the initial group of five patients is 106, while that in the later group is 91 beats per minute. It is felt that this difference is not large enough to be significant. Furthermore, in a more basic sense the circulation

time has been shown to depend upon only two factors, which are the minute output of the heart (cardiac output) and the active volume of blood between the points of injection and detection.[7, 8] Since the heart rate may reflect a true difference in cardiac output, this factor can not be completely discounted in evaluating these results.

Summary and Conclusions

The problem of the identification of venoarterial shunting in congenital heart disease through an over-riding aorta was approached by determination of the circulation time from the right ventricle to the ear. The test was performed during cardiac catheterization and consisted in measuring the time interval between the injection of dye (T-1824) into the right ventricle and its detection in the capillaries of the ear by an oximeter. Eighteen patients were studied. Diagnostic study strongly indicated the probability that an over-riding aorta existed in five of the 18 patients. There was reasonable assurance that no over-riding of the aorta was present in the remaining 13 patients. The average of the circulation times of the first group was 4.0 seconds, with a range of 3.5 to 4.7 seconds. The average of the second group was 7.4 seconds, with a range of 5.3 to 10 seconds. There was thus a considerable difference between the average values in the two groups, and no overlapping of individual values. The factors of age and heart rate probably did not impair the validity of the comparison between the two groups. The importance of localizing the site of venoarterial shunting to an over-riding aorta was discussed as well as the difficulties involved. It is therefore suggested that the finding of a circulation time from the right ventricle to the ear of less than 5 seconds (using the described technic) is strong evidence of a venoarterial shunt through an over-riding aorta. However, final validation of these findings will depend upon future experience with the technic and confirmation from postmortem examinations.

Addendum

A short while after this paper had been submitted for publication, another similar study was reported which was directed toward the same purpose but used a somewhat different technic. The findings were generally consistent with ours.[10]

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Patent Ductus Arteriosus in the Absence of a Continuous Murmur

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The diagnosis of patent ductus arteriosus is difficult when the classic continuous murmur is not present. In infancy, in the presence of cardiac decompensation and when the ductus approximates the aorta in size, the continuous murmur is frequently absent. A correct diagnosis may be important, however, for a large patent ductus arteriosus can cause serious difficulty. Early surgical treatment may be lifesaving. In this series a large patent ductus was associated with pulmonary hypertension, great cardiac enlargement and absence of the continuous murmur. The presence of pulmonary hypertension is further reason for early surgical treatment.

A VAST amount of material has been reported concerning the hemodynamic changes and the clinical syndrome associated with a patent ductus arteriosus. The key clinical signs of a continuous murmur, high pulse pressure, active heart and normal electrocardiogram have been repeatedly stressed by numerous authors.[1–4] The risk of error in diagnosis if the classic continuous murmur is lacking has been emphasized.

Although the absence of a continuous murmur in the pulmonary area casts doubt upon the diagnosis, a large patent ductus may exist without a typical murmur. Indeed, it is well known that a continuous murmur is seldom heard in infancy. Moreover, it may be absent in patients who have pulmonary hypertension or who are in heart failure.[5–8] Nevertheless, a large patent ductus can cause acute cardiac embarrassment and may possibly lead to irreversible pulmonary vascular changes. Therefore, the diagnosis of a large patent ductus in the absence of the characteristic continuous murmur is important.

The purpose of this paper is to present our experience in 24 patients in whom the clinical diagnosis of patent ductus was considered despite the absence of a typical continuous murmur. All these patients were operated on during 1950: of the 24, 15 were proved to have large patent ductuses, two to have aortic septal defects, and seven to have high ventricular septal defects, or hearts of the Eisenmenger type.* This high percentage of diagnostic error prompted us to review this series in a search for better differential points.

The clinical syndrome presented by patients in this series was remarkably uniform despite the distinct differences in the malformation present. The findings usually were: failure to grow and develop normally, repeated episodes of pneumonia, dyspnea, early onset of cardiac failure, usually a high pulse pressure and bounding pulse, splitting and accentuation of the second sound at the base, a systolic murmur along the left sternal border, and commonly an apical rumbling mid-diastolic murmur. Fluoroscopy and x-ray showed a generalized cardiac enlargement and usually specific enlargement of the left auricle, increased pulmonary vascular markings and often a hilar dance. Electrocardiograms usually showed a normal electrical axis and no ventricular hypertrophy in the precordial leads. In those patients catheterized

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*The seven cases of ventricular septal defect reported here in no way resemble the classic case of maladie de Roger. It is extremely difficult to differentiate a large ventricular defect from early Eisenmenger's complex. Indeed, in the one patient studied at autopsy the aorta over-rode the ventricular septal defect to a slight degree. In this paper no effort has been made to differentiate a high ventricular septal defect from an early Eisenmenger's complex. Reference will be to a high ventricular septal defect.

there was always marked pulmonary or right ventricular hypertension.

The following case histories were selected as representative samples.

Case Reports

Case 7. C.U. (H.L.H. A-65001) White male first seen in the Cardiac Clinic in August, 1948, at the age of 9 months.

Past History and Present Illness: He was the result of a normal full-term pregnancy and appeared normal at birth. Easy fatigability and a gradual increase in his respiratory rate were noted when he was 5 months old. During the following months a bulge of the left chest became progressively more prominent. A murmur was first described at 5½ months of age. There was no history of cyanosis or episodes of paroxysmal dyspnea.

Physical Examination: The weight was 17 pounds, 14 ounces and the pulse 125 beats per minute; the blood pressure was not obtained. He was well developed and well nourished with no evidence of cyanosis, clubbing or edema. Breathing was rapid and shallow. There was a bulge of the left side of his chest. No thrill was palpable. The maximal apical impulse was in the fifth left intercostal space outside the midclavicular line. The second heart sound in the pulmonary area was accentuated. There was a rather loud, blowing, medium-pitched, slightly rough, systolic murmur heard over the entire precordium, loudest in the third and fourth left intercostal spaces just to the left of the sternum. Diastole was clear. The lungs were normal. The liver edge was felt at the costal margin.

Fluoroscopy: The heart was globular in shape with a full pulmonary artery segment. There was slight right ventricular enlargement. The auricles were thought to be normal in size. The vascular markings were accentuated and marked pulsations were noted in the hilar vessels.

Blood Findings: Hemoglobin was 13.5 Gm. per 100 cc. The hematocrit was 41.

Electrocardiogram showed tendency to right axis deviation.

Impression: A tentative diagnosis of an auricular septal defect was made.

Course: He was hospitalized in October, 1948, and again in March, 1949, for respiratory infections. On the second admission he developed signs of cardiac failure and was digitalized with but little improvement.

By October, 1950, when he was almost 3 years old, his physical findings had altered considerably. He was small and thin. His pulses were waterhammer in character. The systolic blood pressure was 115; sounds were heard to 0. His heart had enlarged still more; the maximal apical impulse was in the sixth left intercostal space in the anterior axillary line. The second heart sound in the pulmonary area was definitely split. The systolic murmur was coarser and was maximal in the second and third left intercostal spaces. At the apex a rumbling mid-diastolic murmur had developed. The liver extended three fingerbreadths below the right costal margin. On fluoroscopy all the chambers appeared enlarged, particularly the left auricle (fig. 1).

The electrocardiogram had altered and now showed P-R interval 0.16 second. QRS duration 0.07 second, P_1 was wide and notched. The intrinsicoid deflection in V_5 was 0.06 second. Interpretation: left axis deviation. The precordial leads suggested combined ventricular hypertrophy. The abnormal P waves suggested auricular hypertrophy (fig. 2).

At this time he was catheterized by Dr. Richard J. Bing, to whom we are indebted for the use of his material and for the help he has given us in the analysis of the findings of cardiac catheterization.

Oxygen Content	(Vol. %)	Pressures (mm. Hg)
Superior Vena Cava	11.4	
Inferior Vena Cava	12.9	
Right Auricle	12.6	
Right Auricle	11.4	9/7
Right Ventricle — inflow tract	11.5	
Right Ventricle — outflow tract	13.1	48/20—dampened
Main Pulmonary Artery	15.0	
Right Pulmonary Artery	14.7	54/46—dampened
Right Pulmonary Artery	14.1	
Brachial Artery	14.5	
Oxygen Capacity	16.7	
Oxygen Saturation	86.9	

Flows (cc. per minute per square meter)	
Systemic Flow	3800
Pulmonary Flow	5090
Effective Flow	2338

Remarks: The rise in oxygen content from the right ventricular inflow tract to the outflow tract and principally to the pulmonary artery indicated (1) an extracardiac arteriovenous shunt; (2) either an intracardiac arteriovenous shunt or pulmonary regurgitation. The slightly lowered arterial oxygen saturation suggested a small venous-arterial shunt. Pressures obtained from the right ventricle and pulmonary artery indicated a considerable degree of pulmonary hypertension.

Impression: The high pulse pressure, the large left auricle, the electrocardiogram, and the catheterization findings led us to consider a large patent ductus.

Surgery: On October 13, 1950, Dr. Alfred Blalock performed an exploratory left thoracotomy and found a large, thickened pulmonary artery, the pressure within which was markedly elevated. No thrill could be palpated over it or over the region of the

ductus arteriosus. On further dissection a large patent ductus which measured 12 mm. in external diameter was isolated and closed. The aorta measured 18 mm. in diameter proximal to the ductus.

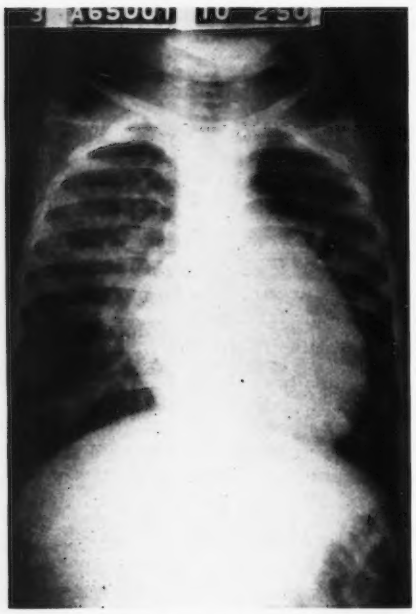

FIG. 1. X-rays of chest, patent ductus arteriosus. Patient C. U., case 7, anterior-posterior, October, 1950. Cardiothoracic ratio 62.5 per cent. Note large pulmonary arteries and vascular appearing lung fields.

improved. Blood pressure was 104/60, respirations 25, pulse 88. Over the base of the heart there was still a moderately loud systolic murmur of questionable significance. The second heart sound in the pulmonary area was still accentuated and split. The electrocardiogram showed normal P waves. The cardiothoracic ratio had decreased from 62.5 per cent to 52 per cent. The heart action was quiet. The left auricle was of normal size. The pulmonary vascular markings had decreased and the hilar dance had disappeared. The left diaphragm was paralyzed and high.

Case 23. K. R. (H.L.H. A-81311) White female first seen in the Cardiac Clinic (October, 1950) at the age of 10 months.

Past History and Present Illness: Normal full-term pregnancy. Birth weight 6 lbs., 5 oz. At a routine examination at three months an enlarged heart and a heart murmur were discovered. Later she had repeated upper respiratory infections and one severe episode of bronchitis. Her weight gain was very slow and at the age of 10 months she had not yet doubled her birth weight. She could sit up only with difficulty. Respirations at times were excessively rapid. There was no history of cyanosis, edema, or paroxysmal dyspnea.

Physical Examination: Weight 11 lbs., 14 oz., respirations 24, pulse 150. She was small and thin with the physical habitus of a 6 month old baby. There was no chest deformity. Femoral and brachial pulsations were bounding in character. The blood pressure was 110/20. The maximal apical impulse was in the fifth left intercostal space just inside the anterior axillary line. Over the entire precordium, but maximal in the second and third left intercostal spaces, there was a grade III, slightly harsh systolic murmur. Diastole was clear. The second heart sound

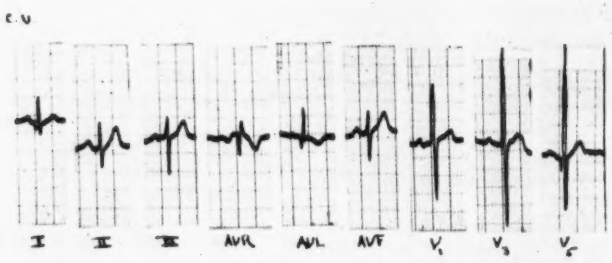

FIG. 2. Electrocardiogram. Patient C.U., case 7. Note left axis deviation.

Following its closure[9] no immediate change of pressure within the pulmonary artery was noted.

Postoperative Course: The child recovered rapidly. Digitalis was discontinued after the tenth day. Six months after surgery he was normally active and had lost his easy fatigability and dyspnea. He had gained six pounds in weight. His appetite was much

in the pulmonary area was accentuated and split. The lungs were clear. The liver edge was felt 1.5 finger breadths below the right costal margin. The liver was not tender and nonpulsatile. The remainder of the physical examination was essentially negative.

Fluoroscopy: The heart was very active and en-

larged (cardiothoracic ratio 64 per cent); there was enlargement of both ventricles, the left auricle and the main pulmonary artery segment. There were increased pulmonary vascular markings and a hilar dance. The aorta was normal in size and position, but was unduly active. X-rays confirmed the fluoroscopic findings (fig. 3).

Blood Findings: Red blood cells were 3.81 million per cu. mm. Hemoglobin was 9 Gm. per 100 cc.

Electrocardiogram: The P-R interval was 0.12 second, The QRS duration 0.05 second. The electrical axis was normal. The T waves in lead I and V_6 were low. Interpretation: The borderline low T waves in lead I and V_6 may have been due to myocardial disease or may have been caused by digitalis. Otherwise the electrocardiograph was within normal limits.

Cardiac catheterization performed by Dr. Richard J. Bing in November, 1950, gave the following data:

Oxygen Content	(Vol. %)	Pressures (mm. Hg)
Superior Vena Cava	9.1	
Inferior Vena Cava	5.4	(near coronary sinus)
Right Auricle	7.0	11/7
Right Ventricle — inflow tract	7.6	62/24
Right Ventricle—apex	8.0	64/16
Femoral Artery	10.7	
Oxygen Capacity	13.4	
Oxygen Saturation	80.9	(confirmed by oximeter)

Remarks: Unfortunately the pulmonary artery was not catheterized. Values for the oxygen content of the blood obtained from the cavae, right auricle and right ventricle did not reveal the presence of any intracardiac shunt. The oxygen saturation of the femoral artery was below normal, suggesting some venous-arterial shunt. Pressure readings from the right ventricle were markedly increased.

Course: While in the hospital she developed bronchopneumonia and cardiac decompensation. She was digitalized and treated intensively with penicillin and Aureomycin. She had recurrent episodes of pneumonitis during the next two months. Finally, after the correction of her anemia by frequent small blood transfusions and when she had been free of infection for a week, we advised surgery believing a patent ductus might be found.

Surgery: On December 18, 1950, Dr. Alfred Blalock performed a left thoracotomy. The left pulmonary artery was much enlarged and thickened, and the pressure within it was markedly elevated. A patent ductus arteriosus was not found. The pericardium was therefore opened and a large aortic septal defect was discovered. During the dissection, a small tear was made in the aorta which was repaired with difficulty. Nothing further could be done and the chest was closed. The patient, however, never regained consciousness and died four hours later.

Autopsy: The heart weight was 70 Gm. (average for this age, 25 to 30 Gm.). There was hypertrophy without appreciable dilatation of both ventricles (RV 5 to 6 mm., LV 8 to 10 mm. in width). Both auricles were dilated, the left more than the right. The foramen ovale was completely sealed. There were no intracardiac defects. The valves were normal. The coronary vessels arose normally. Three or 4 mm. from the origin of the aorta there was a window defect between the aorta and pulmonary artery measuring 1.2 cm. by 1.3 cm. (fig. 4). The main pulmonary artery and its branches were of large caliber with thickened walls. The intrapulmonary vessels were prominent.

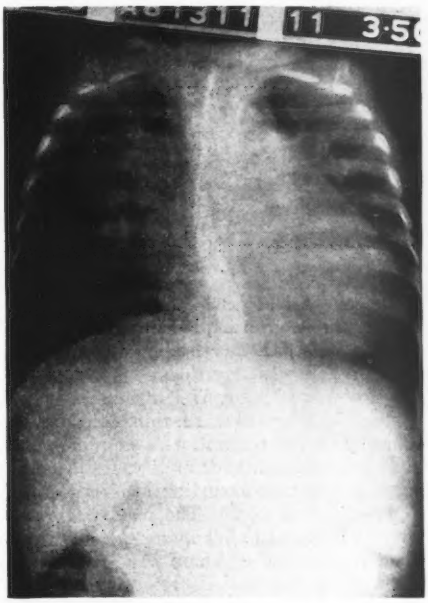

FIG. 3. X-ray of chest, aortic septal defect. Patient K. R., case 23, anterior-posterior. Cardiothoracic ratio 64 per cent. Note vascularity of lung fields, large pulmonary artery.

Microscopic sections of the lungs revealed that the intrapulmonary arteries had a normal distribution. Several of these showed severe intimal proliferation associated with medial thickening. No thrombi were seen. The large pulmonary and bronchial arteries were normal.

Final Diagnosis: (1) Aortic septal defect, (2) cardiac hypertrophy, (3) pulmonary arterial thickening.

Case 16. (H.L.H. A-82007) White female first

seen in the Cardiac Clinic (November, 1950) at the age of 4½ months.

Past History and Present Illness: Full-term normal pregnancy. Birth weight was 7 lbs., 13 oz. She appeared normal at birth. At 6 weeks of age she developed rapid grunting respirations and a heart murmur was heard. Her feeding was difficult and her weight gain was very slow.

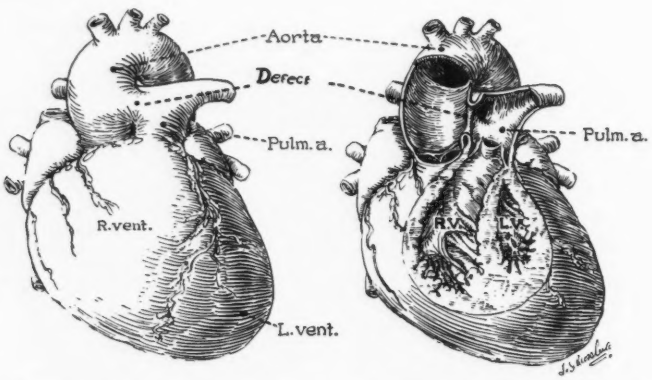

FIG. 4. Drawing of specimen of aortic septal defect. Patient K.R., case 23.

Physical Examination: Weight 9 lbs., respirations 80, pulse 150. She was small, thin, pale, and looked chronically ill. Her respirations were rapid and shallow. There was no chest deformity. Her femoral and brachial pulses were bounding in character with a blood pressure of 90/20. The maximal apical impulse was in the sixth left intercostal space outside the midclavicular line. There was a harsh systolic murmur over the entire precordium which was maximal in the second and third left intercostal spaces. No diastolic murmurs were heard. The second heart sound in the pulmonary area was accentuated and split. The lungs were clear. The liver edge was felt two fingerbreadths below the right costal margin. The liver was firm but did not pulsate. There was no edema or cyanosis.

Fluoroscopy: The heart was grossly enlarged and overactive (cardiothoracic ratio 67 per cent). There was enlargement of both ventricles and both auricles. The left auricle appeared larger than the right. The main pulmonary artery segment was prominent. The pulmonary vascular markings were increased and there was a hilar dance. The aorta appeared normal in size and position but was unduly active. X-rays confirmed the fluoroscopic findings (fig. 5).

Blood Findings: Red blood cells were 4.86 million per cu. mm. Hemoglobin was 12.5 Gm. per 100 cc.

Electrocardiogram: Rate 150. P-R interval 0.12 second, QRS duration 0.05 second, T_1 low. T waves in V_5 and V_6 were diphasic. Intrinsicoid deflection in V_1 was 0.05 second. Interpretation: A tendency to right axis deviation. The delayed intrinsicoid deflection in V_1 suggested right ventricular hypertrophy. The ST-T configuration of lead I, V_5 and V_6 suggested left ventricular strain.

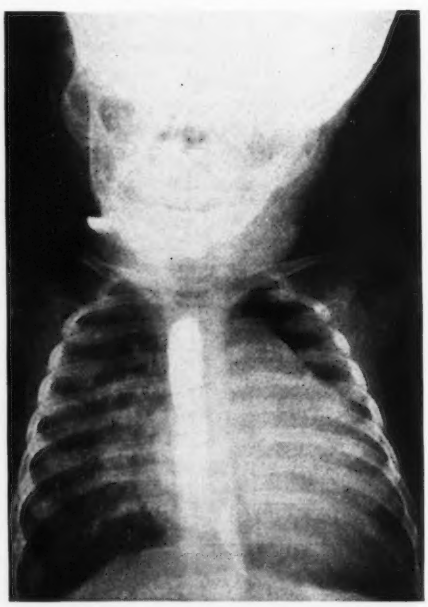

FIG. 5. X-ray of chest, ventricular septal defect. Patient D. H., case 16, anterior-posterior. Cardiothoracic ratio 67 per cent. Note increased vascularity of lung fields and large size of pulmonary arteries.

Course: The patient was digitalized. Following this, her appetite improved but there was no change in the respiratory rate, the size of the heart, or the size of the liver. After five weeks, because of the continued evidence of marked cardiac embarrass-

ment, we advised surgery, believing that she might have a patent ductus arteriosus.

Surgery: On December 22, 1950, Dr. Glenn Morrow performed a left thoracotomy. He found that the pulmonary artery was markedly enlarged and thick-walled and the pressure within it was high. A tiny ductus arteriosus of doubtful patency was found and ligated. The pericardium was then opened, because over the base of the heart and extending along the pulmonary artery a systolic thrill could still be felt. There was no aortic septal defect and the surgeon thought the patient had a high ventricular septal defect. The chest was closed.

Postoperative Course: In the first few days following surgery the patient did well. On the fourteenth day she developed bronchitis and four days later she vomited and aspirated part of her formula. She developed an aspiration pneumonia and died on the nineteenth postoperative day.

Autopsy: The heart and lungs weighed 230 Gm. There was moderate hypertrophy and dilatation of both auricles, the left more than the right. There was a 2 mm. opening in the foramen ovale. The cavae and pulmonary veins were normal, as were the mitral and tricuspid valves. Both ventricles were hypertrophied and dilated. High in the membranous septum there was a defect measuring 8 by 8 mm. This defect opened immediately beneath the septal aortic leaflet. The aorta over-rode this defect by about 10 to 20 per cent. In the right ventricle the defect opened behind the tricuspid valve and proximal to the crista ventricularis. The aortic valve and its leaflets were normal; the valve ring measured 30 mm. in circumference. The ductus arteriosus was atretic. The pulmonary valve ring was dilated, measuring 45 mm. in circumference; the valve leaflets were normal. The main pulmonary artery and its branches were dilated and thickened. Microscopic sections of the lungs revealed that the pulmonary vessels appeared normal in all respects for this age group.

Final Diagnosis: (1) Eisenmenger's complex, (2) cardiac hypertrophy, (3) patent foramen ovale.

Analysis of Clinical Syndrome

These three case histories give a representative picture of the clinical syndrome encountered in this series.

The striking similarities in signs and symptoms, despite the difference in the type of congenital malformation present, make a correct diagnosis difficult. Indeed, among these 24 patients, only 15 proved to have a patent ductus. This is indeed a high incidence of error in diagnosis.

The majority of these patients were young, 19 being under 5 years of age. Most of them were easily fatigued and had exertional dyspnea (see table 1). Pneumonia had occurred in 17. Our youngest patient with a patent ductus (4 months) had acute pulmonary edema. Pulmonary edema and pneumonia, however, give very similar signs in early life and hence the incidence of pulmonary edema may well have been higher. Thirteen were in cardiac failure. Marked cardiac enlargement was the rule, for 17 had cardiothoracic ratios of over 60 per cent. It is worthy of note that the incidence of cardiac failure was lower in the patients with a patent ductus than in the patients with ventricular septal defects, although in general the former had the larger hearts.

Twenty-one patients had high pulse pressures and bounding pulses. The highest pulse pressures occurred in patients with a patent ductus and an aortic septal defect, but many of the patients with ventricular septal defects had high pulse pressures. Furthermore, one patient with a patent ductus had a normal pulse pressure. Thus, the quality of the pulse and the pulse pressure were of no diagnostic aid. The typical continuous machinery murmur was not heard in any of the patients. Our oldest patient with a ventricular defect, aged 11 years, we misdiagnosed as a patent ductus because upon exercise his basal systolic murmur seemed to extend into diastole and his pulse pressure increased. In four others the systolic murmur at times seemed to extend slightly into diastole. Rumbling mid-diastolic murmurs at the apex were heard in 10 patients with a patent ductus and in one with a ventricular septal defect. An apical presystolic murmur was present in two patients with patent ductuses. Systolic murmurs were always present, but the site of maximal intensity varied. The commonest site was in the second and third left intercostal spaces; however, in nine patients with a patent ductus the murmurs were maximal at the lower end of the sternum or at the apex.

Fluoroscopy and x-ray in each instance showed increased pulmonary vascularity, but not always increased hilar pulsations. The main pulmonary artery segments were convex. Generalized cardiac enlargement was the rule; there was definite left auricular enlargement in 13 patients with patent ductus, six with ventricu-

TABLE 1.—*Case Summaries*

Case No.	Age in Years	Weight (lbs)	Symptoms	Pulse and Blood Pressure	Cardiac Findings*	Fluoroscopy*	ECG†	Special Studies	Measurements at Surg. Outside Diameter	Result of Operation
E.C. 1	$\frac{4}{12}$	8	Marked dyspnea; cardiac failure; two episodes of acute pulmonary edema	Pulse, bounding B.P. 90/70	Systolic murmur, 2nd & 3rd LIS; P_2 loud	C/T 58%; pulmonary vascular markings +++	L.A.D. R.V.H.	Arterial O_2 Sat. 76%	Aorta, 8 mm. Ductus, 5 mm.	6 mos. later, well; no murmurs
K.W. 2	$\frac{8}{12}$	10	Moderate dyspnea; easy fatigability; poor weight gain	Pulse, normal B.P. 70/0	Systolic murmur, apex; apical mid-diastolic murmur & diastolic gallop	C/T 63%; vascular markings +++	No A.D. No V.H. L.H.S.	Arterial O_2 Sat. 98% Catheterized‡ Angios	No measurements	6 mos. later, well; no murmurs; C/T, 50%
N.S. 3	$1\frac{6}{12}$	$15\frac{1}{2}$	Moderate dyspnea; easy fatigability	Pulse, full B.P. 98/0	Systolic murmur, 4th & 5th LIS; P_2 loud and split	C/T 58%; hilar pulsations +++	No A.D. No V.H.	Arterial O_2 Sat. 86% Catheterized‡	Aorta, 10 mm. Ductus, 10 mm.	6 mos. later; well; slight systolic murmur, ? functional; C/T, 50%
E.W. 4	$2\frac{3}{12}$	25	Marked dyspnea; cardiac failure; poor response to digitalis	Pulse moderately full; B.P. 100/60	Bulge, left chest; systolic murmur, apex; mid-diastolic rumble; P_2 loud	C/T 66%; hilar pulsations +	R.A.D. R.V.H.	Arterial O_2 Sat. 87% Catheterized‡	Aorta, 12 mm. Ductus, 12 mm.	Died
M.L.B. 5	$2\frac{6}{12}$	21	Marked dyspnea; cardiac failure; fair response to digitalis	Pulse, bounding B.P. 100/10	Bulge, left chest; systolic murmur, base; diastolic blow, sternum; P_2 loud and split	C/T 69%; hilar pulsations ++++	No A.D. No V.H.	Arterial O_2 Sat. 84.9%	Ductus, "very large"	6 mos. later, improved; systolic murmur, suggests IVSD
R.L. 6	$2\frac{9}{12}$	27	Dyspnea; cardiac failure; fair response to digitalis	Pulse, bounding B.P. 90/0	Systolic murmur, 3rd, 4th & 5th LIS; apical diastolic rumble; P_2 loud and split	C/T 60%; hilar pulsations ++++	No A.D. L.V.H.	None	Ductus, 12 mm.	No murmurs; well
C.U. 7	$2\frac{11}{12}$	$32\frac{1}{2}$	Moderate dyspnea; cardiac failure; poor response to digitalis	Pulse, bounding B.P. 115/0	Bulge, left chest; systolic murmur, base; apical mid-diastolic; P_2 loud and split	C/T 63%; hilar pulsations ++	L.A.D. C.V.H.	Arterial O_2 Sat. 87% Catheterized‡	Aorta, 18 mm. Ductus, 12 mm.	6 mos. later, much better; systolic murmur; C/T 52%
N.B. 8	$3\frac{8}{12}$	36	Moderate dyspnea; easy fatigability	Pulse, full B.P. 100/60/0	Bulge, left chest; systolic murmur, base; diastolic blow, base; P_2 loud and split	C/T 58%; hilar pulsations +++	R.A.D. C.V.H.	Arterial O_2 Sat. 92% Ductus catheterized‡	Aorta, 15 mm. Ductus, 10 mm.	3 mos. later, well; faint systolic
B.H. 9	$3\frac{1}{12}$	$28\frac{1}{2}$	Moderate dyspnea; cardiac failure; poor	Pulse, bounding B.P.	Bulge, left chest; systolic & diastolic	C/T 66%; hilar pulsations	No A.D. No V.H.	Arterial O_2 Sat. 85%	Ductus, 10 mm.	Recanalization; now has con-

B.H. 9	$3\frac{1}{12}$	$28\frac{4}{7}$	Moderate dyspnea; cardiac failure; poor response to digitalis	Pulse, bounding B.P. 126/50/0	Bulge, left chest; systolic & diastolic, apex; blowing systolic, base; P_2 loud	C/T 66%; hilar pulsations ++++	No A.D. No V.H.	Arterial O_2 Sat. 85% Ductus catheterized‡	Ductus, 10 mm.	Recanalization; now has continuous murmur
S.G. 10	4	26	Moderate dyspnea; easy fatigability	Pulse, full B.P. 80/0	Rumbling apical diastolic; ? continuous, 2nd RIS; P_2 loud and split	C/T 60%; hilar pulsations ++	No A.D. No V.H. R.H.S.	Arterial O_2 Sat. 94% Ductus catheterized‡	Ductus, 10 mm.	4 mos. later, well; no murmurs
B.R. 11	4	30	Moderate dyspnea; easy fatigability	Pulse, full B.P. 100/40	Bulge, left chest; systolic murmur, 4th LIS; apical mid-diastolic ? presystolic apex	C/T 63%; hilar pulsations ++++	No A.D. No V.H.	Arterial O_2 Sat. 96% Ductus catheterized‡	Ductus, 10 mm.	4 mos. later, well; faint functional systolic
R.C. 12	$5\frac{5}{12}$	36	Dyspnea; cardiac failure; fair response to digitalis	Pulse, bounding B.P. 104/50/20	Systolic murmur; apical systolic and presystolic; P_2 loud and split	C/T 62%; hilar pulsations +	L.A.D. No V.H. L.H.S.	Arterial O_2 Sat. 90% Ductus catheterized‡	Aorta, 18 mm. Ductus, 12 mm.	3 mos. later, well; faint functional systolic
A.E. 13	$5\frac{6}{12}$	30	Moderate dyspnea; easy fatigability	Pulse, bounding B.P. 100/45/20	Bulge, left chest; systolic murmur, 3rd, 4th & 5th LIS; P_2 loud and split	C/T 65%; hilar pulsations ++	No A.D. No V.H.	Arterial O_2 Sat. 96% Catheterized‡	Ductus, 16 mm.	Recanalized; died 6 mos. later, removal of aneurysm
P.P. 14	6	30	Moderate dyspnea; easy fatigability	Pulse, bounding B.P. 88/0	Systolic & diastolic, 2nd & 3rd LIS, ? continuous 2nd RIS; P_2 loud and split	C/T 66%; hilar pulsations +	R.A.D. Combined V.H.	None	Ductus, 13 mm.	5 mos. later, heart small but recanalized ductus-typical murmur
B.W. 15	$8\frac{6}{12}$	73	Easy fatigability; suspect rheumatic fever	Pulse, full B.P. 100/50	Systolic murmur, 3rd LIS; P_2 loud and split	C/T 58.8%; hilar pulsations +++	L.A.D. L.V.H.	Arterial O_2 Sat. 87.8% Catheterized‡	Ductus, 12 mm.	4 mos. later, much improved; still systolic murmur, 3rd LIS
High Ventricular Septal Defect										
D.H. 16	$\frac{5}{12}$	9	Marked dyspnea; cardiac failure; poor response to digitalis	Pulse, bounding B.P. 92/20	Systolic murmur; 2nd LIS; P_2 loud and split	C/T 67%; hilar pulsations ++++	R.A.D. R.V.H. L.H.S.	None	None	Died, 19 days postoperatively; aspiration pneumonia

* LIS—Left intercostal space; RIS—Right intercostal space; P_2—Second pulmonary heart sound; C/T—Cardiothoracic ratio.

† I.A.—Indeterminate axis; L.A.D.—Left axis deviation; R.A.D. Right axis deviation; L.V.H.—Left ventricular hypertrophy; R.V.H.—Right ventricular hypertrophy; C.V.H.—Combined ventricular hypertrophy; L.H.S.—Left heart strain; R.H.S.—Right heart strain.

‡ For results of catheterization, see table 2.

TABLE 1.—*Continued*

Case No.	Age in Years	Weight (lbs)	Symptoms	Pulse and Blood Pressure	Cardiac Findings*	Fluoroscopy*	ECG†	Special Studies	Measurements at Surg. Outside Diameter	Result of Operation
A.B. 17	$1\frac{5}{12}$	25	Moderate dyspnea; cardiac failure; fair response to digitalis	Pulse bounding B.P. 130/50/0	Bulge, left chest; systolic murmur, 4th & 5th LIS; P_2 loud and clear	C/T 63%; hilar pulsations ++++	No A.D. No V.H.	Catheterization attempted	Ductus, 2 mm. ? patent	Unchanged
E.P. 18	$1\frac{5}{12}$	18	Moderate dyspnea; cardiac failure; fair response to digitalis	Pulse, full B.P. 96/20	Systolic murmur, 3rd & 4th LIS; rumbling apical diastolic; P_2 loud and split	C/T 64%; hilar pulsations +++	I.A. R.V.H.	Arterial O_2 Sat. 94% Catheterized‡	None	Unchanged
L.L.M. 19	2	21	Marked dyspnea; cardiac failure; poor response to digitalis	Pulse, bounding B.P. 125/70/0	Systolic murmur, 3rd & 4th LIS; P_2 loud and split; liver pulsating	C/T 75%; hilar pulsations ++++	R.A.D. R.V.H.	Arterial O_2 Sat. 89.8% Catheterized‡	Ductus, 3 mm. ? patent	Unchanged
J.L. 20	$2\frac{5}{12}$	29	Moderate dyspnea; cardiac failure; fair response to digitalis	Pulse, full B.P. 88/58	Bulge, left chest; systolic 4th LIS; diastolic rumble, 4th LIS; P_2 loud and split	C/T 55%; hilar pulsations ++++	R.A.D. R.V.H.	Arterial O_2 Sat. 91.4% Catheterized‡	Ductus, 2 mm. ? patent	Unchanged
S.S. 21	$4\frac{6}{12}$	36	Easy fatigability; ? dyspnea	Pulse, mod. full; B.P. 110/75/55	Systolic murmur, 1st & 2nd LIS; diastolic rumble, 3rd LIS.	C/T 54%; hilar pulsations +++	No A.D. No. VH. L.H.S.	None	None	Unchanged
T.H. 22	$11\frac{9}{12}$	79	Slight dyspnea; slight fatigability	Pulse, sl. full B.P. 110/70	Systolic murmur, 2nd LIS; ? continuation into diastole	C/T 48%; hilar pulsations +	No A.D. No V.H.	None	None	Unchanged
					Aortic Septal Defect					
K.R. 23	1	12	Marked dyspnea; cardiac failure; poor response to digitalis	Pulse, bounding B.P. 110/20	Systolic murmur, 2nd & 3rd LIS; P_2 loud and split	C/T 64%; hilar pulsations ++++	No A.D. No V.H.	Arterial O_2 Sat. 80% Catheterized‡	None	Died following surgery, hemorrhage and shock
P.P. 24	$4\frac{9}{12}$	35	Marked dyspnea; slight cyanosis; easy fatigability	Pulse, bounding B.P. 92/10	Bulge, left chest; systolic murmur, 3rd LIS; Diastolic blow, base	C/T 62%; hilar pulsations +++ right aortic arch	R.A.D. No V.H.	Arterial O_2 Sat. 96% Catheterized‡	None	Unchanged

lar defect, and both patients with an aortic septal defect. Usually both ventricles were enlarged.

The electrocardiographic findings were in no way uniform. Numerous variations of electrical axis, ventricular hypertrophy and strain patterns were seen. In general, the electrocardiogram showed a balanced electrical axis and no evidence of ventricular hypertrophy. Because of the number of variations encountered, we do not feel that any conclusions can be drawn. However, although this series is small, it is worthy of note that no patients with ventricular or aortic defects showed left axis deviation or left ventricular hypertrophy in the precordial leads, although two ventricular defects showed a left heart strain pattern. The two patients with a patent ductus who showed right ventricular hypertrophy were the 4 month old infant, and one who died and who was found to have, in addition to a large patent ductus, a congenital malformation of the mitral valve. (See table 1.)

TABLE 2.—*Cardiac Catheterization Results*

Patent Ductus Arteriosus

Name	Age		(Vols. %) Rise in Oxygen Content From:				Arterial Oxygen Saturation, %	Pressures (Mm. Hg.)			LV output passing thru defect, %
	Yrs.	Mos.	Cavae to RA	RA to RV-in	RV-in to RV-out	RV-out to PA		RV	PA	Mean PA	
K.W.		8	0	0	0	4.45	98	80/58‡	118/108‡	114	75.5
N.S.	1	6	0	0	0.44	2.67	88	70/57‡	90/82‡	85	55
E.W.*	2	2	0.60	0.7	0.48	2.61	87	70/17	70/56	66	66
M.L.B.	2	6	0	0	0	1.97	84	44/29‡	54/44‡	50	42.7
C.U.	2	11	0	0	1.56	1.91	86.9	48/20‡	54/46‡	52	54
N.B.†	3	8	0	0	.7	.7	91.9	102/18	97/74	90	37
B.H.†	3	11	0	0	0	4.3	85.5	53/49‡	80/70‡	76	?
B.R.†	4		no sample	?	?	no sample	96	46/38‡	?	?	?
S.G.†	4		0	0	0.4	0.96	94	72/2	73/44	64	44.6
R.C.†	5	5	0	0	0	3.4	90	80/4	72/48	64	?
A.E.*	5	6	0	0	0	2.65	96	93/0	86/67	79	50.5
B.W.	8	6	0	1.1	0.59	0.1	87.8	96/0	74/64	71	38.8
High Ventricular Septal Defect											
											Left to right shunt
E.P.	1	5	?	1.77	?	No PA sample	94	34/11‡	?	?	70
L.L.M.	2		1.40	0	0	1.00	89.8	52/13‡	42/27‡	37	53
J.L.	2	5	0	1.30	1.60	0	91.4	60/16	51/32	44	62
Aortic Septal Defect											
K.R.*	1		0	0	0.36	No PA sample	81	64/16	?	?	?
P.P.	4	9	0	0	0	3.76	87.3	67/36‡	87/72	82	46.2

* Confirmed at Autopsy
† Ductus catheterized
‡ Dampened Pressure Readings

Cardiac catheterization (table 2) was performed in 17 cases. Every patient had marked right ventricular or pulmonary arterial hypertension. In 10 of the 11 patients with a patent ductus who were catheterized, there was a significant rise of oxygen content on passing from the right ventricle to the pulmonary artery. In five patients the catheter was passed through the ductus into the descending aorta and thus

confirmed the diagnosis of patency of the ductus. This high incidence of intubation of the ductus is perhaps explained by the large size of the ductuses and the pulmonary hypertension. Cardiac catheterization. however, is not infallible. An aortic septal defect gives the same findings as a patent ductus arteriosus. Furthermore, when a patent ductus is complicated by pulmonary regurgitation, the findings are very similar to those in a ventricular defect. A ventricular defect may also be confused with a patent ductus arteriosus if the blood sample from the outflow tract of the right ventricle is not taken close to the pulmonary valve in the stream of blood passing through the defect from the left ventricle to the pulmonary artery.

Results of Operation

The mortality rate in this series is high. Four patients died as a result of operation. Two died within 24 hours of surgery, one, a patient with a patent ductus (case 4) and one patient with an aortic septal defect (case 24). There were two late deaths; one patient with a ventricular septal defect who died 19 days after surgery from aspiration pneumonia (case 9), and another patient who died six months after the closure of the ductus, during a second operation undertaken in an attempt to remove an infected aneurysm which had developed in and around the ductus (case 13).

The 13 with patency of the ductus arteriosus who survived have been greatly helped. Those in heart failure improved rapidly, and all are living normal active lives. In every one there has been a marked decrease in heart size. The diastolic murmurs disappeared in all in the immediate postoperative period. Examination six months postoperatively revealed that three patients (cases 9, 13, 14) had developed typical continuous murmurs in the pulmonary area, suggesting recanalization of the ductus. Three other patients (cases 5, 7, 15) had loud systolic murmurs and thrills in the third and fourth left intercostal spaces close to the sternum, suggestive of additional malformations, probably small ventricular defects. Two other patients had soft, high-pitched systolic murmurs over the precordium which might be functional. Further follow-up is necessary before we can be certain as to the presence or absence of additional cardiac malformations in these last five patients.

Discussion

The most significant findings in the patients with a patent ductus were the marked degree of pulmonary hypertension found by catheterization and at surgery, and the unusually large ductus arteriosus which approximated the aorta in size (see table 3).

An accurate comparison of brachial and pulmonary arterial blood pressures is not possible, since pressures were not recorded simultaneously, and because the pulmonary arterial pressures were measured by a strain gage manometer and the brachial arterial pressures by a sphygmomanometer. The direct pulmonary arterial recordings were often dampened. Nonetheless, a comparison of the pressures in the pulmonary and systemic circulations is of value (table 3). In most instances the systolic pressure in the systemic circulation was significantly higher than that in the pulmonary circulation. On the other hand, the diastolic pressure in the systemic circulation was approximately the same as that of the pulmonary circulation. This suggests that the flow of blood through the ductus took place during systole, which is in

Table 3.—*Pulmonary and Brachial Artery Pressures by Cardiac Catheterization in Patients with a Large Patent Ductus Arteriosus*

Name	Age		Cuff Brachial Artery Pressure	Direct Pulmonary Artery Pressure
	Yrs.	Mos.		
E.C. #1		4	90/70	—
K.W. #2		8	70/0	118/108, 80/70
N.S. #3	1	6	98/0	90/82
E.W. #4	2	2	100/60	70/56
R.L. #5	2	9	90/0	—
M.L.B. #6	2	6	100/10	54/44
C.U. #7	2	11	115/0	54/46
N.B. #8	3	8	100/60/0	97/74
B.H. #9	3	11	126/50/0	80/70
B.R. #10	4		100/40	—
S.G. #11	4		80/0	73/44
R.C. #12	5	5	104/50/20	72/48
A.E. #13	5	6	100/45/20	86/67
P.P. #14	6		88/0	—
B.W. #15	8	6	100/50	74/64

accord with the presence of a systolic murmur and the absence of a continuous murmur.

Although the main flow of blood through the ductus was limited to systole, it is of interest to note the high percentage of the left ventricular output which passed through the ductus. (Refer to table 2.) The average percentage of left ventricular output passing through the ductus in the patients in whom these flows could be calculated was over 50 per cent.

Dr. Alfred Blalock has stated that the usual patent ductus found in older children measures 4 to 8 mm. in diameter and is small in comparison with the size of the aorta.[10] In all our cases, except the youngest, aged 4 months, the ductus measured over 10 mm. in diameter and approximated the size of the aorta. It seems likely in these patients that the large size of the ductus was the cause of the high degree of cardiac embarrassment and the great cardiac enlargement.

A sharp drop in pulmonary arterial pressure was not observed immediately after closure of the ductus. In one patient at operation there was a drop of systolic pressure from 81 to 66 mm. Hg. However, our previous experience and that of others[11] suggests that pulmonary arterial pressure drops slowly over a period of months after closure of the ductus.

The continuous murmur associated with patency of the ductus arteriosus is thought to be due to a continuous flow of blood through the ductus from the aorta into the pulmonary artery. As Taussig states,[3] such a flow of blood is dependent upon a difference in systolic and diastolic pressures between the systemic and pulmonary circulations. In the neonatal period and early infancy, the systemic pressure is low and the pulmonary arterial pressure is relatively high.[12, 13] The blood flow through the ductus in this age group, therefore, will be minimal or nonexistent and no murmur will be audible. With the growth of the infant, the systemic pressure rises. Studies of the pulmonary vascular bed during infancy with special reference to the size of the smaller pulmonary arteries by Civin and Edwards[14] suggest that, under normal conditions, pulmonary resistance and hence pulmonary arterial pressure fall gradually during the first six to seven months of life. The rise in systemic pressure and the gradual fall in pulmonary arterial pressure results in a flow of blood through the ductus arteriosus. The blood flow at first will be only during systole and the murmur will be purely systolic. When the systemic diastolic pressure becomes greater than the pulmonary diastolic pressure, the blood flow through the patent ductus will be continuous and the murmur will assume its characteristic continuous quality. Usually this continuous murmur appears about the age of two to three years. In the presence of pulmonary hypertension, however, the onset of the continuous murmur will be delayed until the systemic pressure has risen to a proportionately higher level.[3] Dr. Helen Taussig[15] has observed a number of patients with a patent ductus and a large heart who have not developed a continuous murmur until the age of five or six.

The development of a continuous murmur in the two patients in whom we think recanalization has occurred and in the child who developed an aneurysm and continuous murmur and died at the time of the second operation suggests that during the period when their ductuses were occluded, the pressure in the pulmonary arteries fell. Hence, with recanalization of the ductus, the pressure gradient between the aorta and the pulmonary arteries was sufficient to produce a continuous flow of blood through the ductus and a continuous murmur.

In case 13 an interesting series of changes took place. The child, prior to the closure of the ductus, had a systolic murmur in the third and fourth left intercostal space, a blood pressure of 100/45, and a cardiothoracic ratio of 65 per cent. Following suture ligation of the ductus the murmur disappeared, the blood pressure became 100/80, and the cardiothoracic ratio fell to 50 per cent. With recanalization of the ductus and aneurysm formation she developed a continuous murmur typical in every respect of the murmur usually associated with a patent ductus. Her blood pressure was 100/0; her cardiothoracic ratio did not change. At the time of the first operation pulmonary hypertension (87/67 mm. Hg by catheterization) and a ductus 16 mm. in diameter were found. At the time of the second operation, there was no pulmo-

nary hypertension, and the ductus had a very small lumen. In this patient the association of a large patent ductus almost the size of the aorta with pulmonary hypertension and an absence of a continuous murmur is very strikingly demonstrated.

There is increasing evidence that prolonged pulmonary hypertension causes secondary changes in the pulmonary vascular bed.[16] These changes probably cause a further rise in the pulmonary arterial pressure as well as a fixed irreversible resistance. The pulmonary arterial pressure may increase to such an extent that it exceeds the aortic pressure and consequently blood flow through a patent ductus arteriosus will be from pulmonary artery to aorta.[17–20]

Edwards[21, 22] and Civin and Edwards[23] have advanced the hypothesis that under certain conditions the pulmonary vascular bed may retain its fetal characteristics, that is, thick-walled, muscular pulmonary arteries with thickened media and adventitia and a small lumen. In Eisenmenger's complex, single ventricle with a large pulmonary artery, patent ductus arteriosus combined with coarctation of the aorta, true truncus arteriosus and other malformations, a high resistance must be maintained in the pulmonary vascular bed in order that some blood may pass to the systemic circulation. In the above-mentioned malformations, if the pulmonary vascular bed were to undergo its normal development after birth, the systemic circulation could not be maintained. This may also be true in an infant with a large patent ductus. The persistence of the fetal characteristics of the pulmonary vascular bed prevents the excessive flow of blood from the systemic to the pulmonary circulation.

Edwards also postulates that the increased pulmonary vascular resistance at first is compensatory. As a result, however, of prolonged pulmonary hypertension, changes occur in the intima of the smaller muscular pulmonary arteries which raise the pulmonary resistance and cause it to become irreversible. At what age these changes become irreversible is not known.[24] If the resistance is irreversible, surgical closure of a patent ductus is no longer curative.[25] Indeed, if blood flow through the ductus is primarily from pulmonary artery to aorta, closure of the ductus is contraindicated since the ductus is acting as an escape valve.[17] Therefore, the occurrence of pulmonary hypertension offers a strong argument for early closure of a patent ductus in order to prevent possible irreversible pulmonary vascular changes.

The need for more accurate diagnosis is evident from the high incidence of diagnostic errors in this series. Differential diagnosis is difficult. Angiocardiography was attempted in only one patient (K. W.). In that patient the reopacification of the pulmonary arteries suggested a left to right shunt. The location of the shunt, however, could not be determined. Recent experience in the Cardiac Clinic suggests that angiocardiography may be of aid in the diagnosis of patent ductus with pulmonary hypertension.[26] Opacification of the descending aorta immediately after or simultaneously with the main pulmonary arteries suggests a shunt through a patent ductus from pulmonary artery to aorta.

Keith[27] has recently reported the value of retrograde aortography in infants with a patent ductus arteriosus by the demonstration of the filling of the pulmonary arteries directly from the aorta. This procedure has proved of great value in a later series of patients diagnosed and treated at the U. C. L. A. School of Medicine.

The high mortality rate emphasizes the risks of an exploratory thoracotomy. Therefore, every effort should first be made to reach a definitive diagnosis. Cardiac catheterization has proved of real aid. Retrograde aortography recently has proved the most helpful. Operation should not be undertaken in patients in whom the diagnosis of patent ductus arteriosus is suspected, but not definitively proved, unless the child is in heart failure which does not respond to medical measures, or unless there is good evidence of great cardiac enlargement, extremely vascular lung fields, and pulmonary hypertension.

Summary

The diagnosis of patency of the ductus arteriosus in the absence of a continuous murmur

is difficult. Twenty-four patients were suspected of having patent ductuses without the characteristic continuous machinery murmur. These patients showed failure to grow and develop normally, repeated episodes of pneumonia, dyspnea, early onset of cardiac failure, usually a high pulse pressure and a bounding pulse, splitting and accentuation of the second heart sound at the base, a systolic murmur along the left sternal border and commonly an apical rumbling mid-diastolic murmur. Fluoroscopy and x-ray showed an enlarged heart, especially the left auricle, increased pulmonary vascular markings and often a hilar dance. Electrocardiography frequently showed a normal electrical axis, and no ventricular hypertrophy in the precordial leads. In those patients catheterized there was marked pulmonary or right ventricular hypertension.

Fifteen patients were proved to have large patent ductuses which approximated the size of the aorta. Two patients had aortic septal defects, and seven were diagnosed at surgery as having either high ventricular defects or Eisenmenger complex. There were four fatalities. The 13 patients with patent ductuses who survived surgery were greatly helped.

Catheterization and aortography have been the most helpful in the differentiation of the patent ductuses from the others. Of the 11 patients with patent ductuses catheterized, the ductus itself was catheterized five times, and in 10 patients there was a significant rise in the oxygen content of the blood, on passing from the right ventricle to the pulmonary artery.

The association of a large patent ductus approximating the size of the aorta, pulmonary hypertension, absence of a continuous murmur, and great cardiac enlargement is striking. Pulmonary hypertension, when associated with patency of the ductus arteriosus, may be compensatory in early life. However, long continued pulmonary hypertension may lead to irreversible changes in the pulmonary vascular bed. This affords strong argument for early closure of a large patent ductus arteriosus.

There is need for more accurate diagnosis. The risks of an exploratory thoracotomy are considerable.

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Studies on the Use of Dioxyline Phosphate in the Treatment of Angina Pectoris

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Dioxyline phosphate, on the basis of pharmacologic studies, appeared to be worthy of trial in the treatment of the anginal syndrome. The patients were studied during a control period and during alternate periods of placebo and dioxyline phosphate administration. Exercise tolerance tests were performed during each of the three periods of observation. The dosage of dioxyline phosphate was 800 mg. per day orally. Five of the 12 patients with angina experienced fewer pains while taking dioxyline phosphate than they did during either the control period or the period of placebo administration. The low incidence of serious side reactions was a conspicuous feature of the study.

PAPAVERINE was first suggested for the treatment of angina pectoris by Pal in 1913.[1] Experimentally it was shown to be a good coronary vasodilator in the dog.[2] Elek and Katz,[3] using a higher dosage of papaverine than had been used by previous investigators,[4] reported very favorable results in patients with angina. It was therefore recommended and widely used in the prophylaxis and treatment of anginal attacks. More recent clinical studies, however, have shown it to be of little or no more value than placebo.[5] Additional, probably unwarranted, criticism of papaverine has been the possibility of addiction, since it is an alkaloid of opium.[3]

Recently, a synthetic compound, which is similar to papaverine in chemical structure, has been reported by Henderson, Shipley, and Chen.[6] This compound chemically is 6,7-dimethoxy - 7 - (4′ - ethoxy - 3′ - methoxybenzyl)-3-methyl-isoquinoline. It differs from papaverine in that a methyl group has been placed in position 3 in the isoquinoline ring and an ethoxy group has been substituted for one of the methoxy groups of the benzyl ring. It possesses many of the pharmacologic properties of papaverine and causes relaxation of smooth muscle. Both the hydrochloride and phosphate salts of this compound were studied and no significant difference in dilator properties were found. These workers measured its potency as a vasodilator on the coronary blood flow in dogs. They found that, when compared on the basis of equal amounts injected intra-arterially, the new compound caused coronary dilatation of a degree and duration equal to that of papaverine in four dogs and 5 per cent to 25 per cent greater in four other dogs. The acute toxicity of dioxyline phosphate is about one-fourth that of papaverine as measured by the intravenous injection in mice. Studies also showed the new papaverine alkaloid to have no analgesic action and no tolerance development in experimental animals by repeated administration.

Because the toxicity of dioxyline phosphate is less than that of papaverine it has been suggested that perhaps larger quantities of the former could be used in clinical medicine.[6] An added important aspect of the new drug is that it will not be considered a narcotic.[7] Henderson, Shipley, and Chen, on the basis of their pharmacologic studies, stated that they believed the compound warranted clinical trial.[6]

The present study was therefore begun to attempt a clinical evaluation of the effectiveness of the new isoquinoline derivative in patients with angina pectoris.

METHODS AND MATERIALS

Twelve patients with well established angina pectoris were chosen from the Cardiac Clinic at the Cincinnati General Hospital. The majority of these patients had been under observation in the clinic for several years for angina pectoris and various

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The dioxyline phosphate (Paveril Phosphate) used in this study was supplied by Eli Lilly and Company, Indianapolis, Ind.

medications had been used in the management of their pain.

Each patient kept a small card made in the form of a calendar on which he entered the number of pains experienced each day. All patients were allowed to take nitroglycerin tablets whenever needed. Some of the group were on digitalis and administration of this was continued.

TABLE 1.—*Effect of the Oral Administration of Dioxyline Phosphate on the Number of Anginal Attacks*

Patient	Periods of Study					
	Control		Placebo		Dioxyline Phosphate	
	Weeks	Average No. Attacks per wk.	Weeks	Average No. Attacks per wk.	Weeks	Average No. Attacks per wk.
A. H.	4	1.8 (1–2)	6	1.5 (0–1)	7	0.6 (0–1)
C. N.	8	3.3 (0–7)	6	4.7 (1–16)	6	1.7 (0–8)
J. D.	6	6.3 (0–19)	6	1.7 (0–5)	8	0.4 (0–1)
M. M.	7	23.3 (12–36)	6	19.3 (11–32)	6	14.7 (6–29)
J. M.	8	15.8 (14–17)	15	12.5 (10–17)	6	9.1 (9–11)
N. G.	6	0.5 (0–1)	6	0.2 (0–1)	6	0.5 (0–3)
R. H.	7	1.4 (0–7)	8	0 (0)	6	0.2 (0–1)
G. S.	7	0.3 (0–1)	8	0.5 (0–3)	8	0.5 (0–1)
M. Wil.	7	0.4 (0–1)	6	1 (0–4)	10	0.6 (0–2)
M. O.	14	12.9 (5–18)	6	20.2 (16–32)	8	16.4 (12–21)
E. C.	3	12 (10–17)	5	4 (2–7)	7	3 (1–10)
D. H.	5	10.4 (7–12)	6	14.2 (12–15)	8	13.3 (12–14)

The figures in parentheses indicate the range of attacks per week.

The study was divided into three parts. The first part consisted of a control period of observation from six to eight weeks.

Electrocardiograms consisting of three standard leads, three augmented unipolar limb leads, and the six precordial leads were taken on all patients during the control period. Two patients had normal records, one had left bundle branch block, two had the pattern of left ventricular hypertrophy, six had the pattern of nonspecific myocardial damage, and one had an intraventricular conduction defect. During this control period two exercise tolerance tests were carried out on different days. The patient walked over two steps with an ice cube in each hand up to the point of angina or severe dyspnea.[8–10] If no end point was reached the test was terminated after the patient had performed the recommended number of trips for his age and weight as described by Master.[11, 12] An electrocardiogram, including standard leads, unipolar extremity leads and precordial leads V_4 and V_5 was taken prior to and immediately after completion of the exercise.

The second part consisted of a period of six to eight weeks during which the patient was given either chocolate-coated dioxyline phosphate tablets (200 mg.) four times daily, or a chocolate-coated placebo identical in shape and size. Neither the patient nor the attending physician knew the identity of the preparation administered. At the end of this second period of study another exercise tolerance test was performed as described above.

The third phase consisted of a period of six to eight weeks during which the preparation was switched so that those patients who had been on placebo were now placed on dioxyline phosphate and vice versa. Upon completion of this final phase another exercise tolerance test was performed.

RESULTS

Five of the 12 patients experienced fewer pains while taking dioxyline phosphate than they did during either the control period or while taking placebo (table 1). Three of these patients (A. H., C. N., and J. D.) experienced a reduction of more than 50 per cent in the number of their pains while two (M. M. and J. M.) had a reduction of between 20 per cent and 25 per cent in the number of their pains.

Seven of the 12 patients showed no significant decrease in the number of their anginal pains while taking dioxyline phosphate. In two of these cases their pains were least frequent while on placebo therapy (table 1).

The patients in this study can be divided into three categories on the basis of the severity of their angina during the control period. We shall arbitrarily take an average of fewer than two attacks of pain per week as indicating mild angina (five cases). Those patients with more than an average of two but less than ten attacks of pain per week can be classed as moderate angina (two cases). And, finally, those with more than ten episodes of pain per week can be called severe angina (five cases). Analyzing our results according to the severity of the angina, we find one of those with mild

angina showed improvement on dioxyline phosphate, two of those with moderate angina showed improvement and two of those with severe angina showed improvement.

Statistical analysis of the number of attacks observed during the control period and while receiving the placebo revealed a mean difference of 0.72 attacks for 12 subjects, being less with the placebo than in the control period; the difference was not statistically significant (t = .62, p = 0.6). In comparing the number of attacks during the placebo and with the test drug, a statistically significant difference was observed (t = 3.27, p = <0.01). In this group there was a mean difference of 1.58 attacks, there being fewer attacks in the drug treated group. Statistical analysis of the control period and the drug treated period revealed an average of 2.3 fewer attacks in the drug treated period. However, this was not a statistically significant difference (t = 1.88, p = 0.1). It may seem paradoxical that the difference observed between the drug and control periods was not statistically significant when the mean difference in number of attacks was greater between the test drug and control periods than between the drug and placebo periods. The reason for this is that there was a wider scatter on both sides of the mean difference for the test drug and control periods than for the test drug and placebo periods.

Exercise Tolerance Tests

Exercise tests were performed 53 times on the 12 patients. A positive test as indicated by the occurrence of angina or severe dyspnea was obtained in eight of these patients during the control period. A positive test as indicated by RS-T segment depression of 0.5 mm. or more in standard leads I or II, in the precordial leads, or in aV_L or aV_F, a change in direction of the T waves, or the appearance of conduction defects was obtained in eight patients. At the time of the test, four of these patients with positive tests were on digitalis medication, a fact which renders interpretation doubtful.

Exercise tests were performed on every patient following placebo therapy. Following the course of dioxyline phosphate treatment each patient was given an exercise tolerance test with the exception of one patient (N. G.) who will be discussed below. Only one of the 11 cases tested showed any increased ability to make more trips before experiencing angina or severe dyspnea while on dioxyline phosphate medication than either during the control period or while on placebo tablets. This patient (C. N.) was forced by dyspnea to stop during both the control period and the period of placebo administration. He performed 19 and 14 trips during the control period and 29 during the period of placebo medication. However, following dioxyline phosphate therapy he was able to perform a double Master test (32 trips); he developed dyspnea but it was not severe enough to cause him to stop.

Only one of the nine patients (J. D.) who had a positive exercise test as indicated by the electrocardiographic changes mentioned above showed a negative test after dioxyline phosphate.

One patient (N. G.) after being on dioxyline phosphate six weeks experienced severe precordial pain radiating to the left shoulder and also to the right arm. The pain was not relieved by nitroglycerin. He was admitted to the Cincinnati General Hospital. The electrocardiogram was interpreted as showing subepicardial ischemia. He was given anticoagulants and discharged after six weeks. No exercise tolerance test, therefore, could be performed at the completion of his course of dioxyline phosphate.

Side Effects

Five of the 12 patients experienced unpleasant side effects while on dioxyline phosphate. Two patients (E. C. and G. S.) complained of nausea on the first day of treatment but had no further untoward effects. One patient (R. H.) was nauseated and felt weak and tired for the first two days of treatment; he subsequently had no further complaints. This same patient during a subsequent course of dioxyline phosphate therapy had no side effects except occasional slight epigastric burning. A fourth patient (N. G.) complained of occasional gaseous distension with slight nausea while on dioxyline phosphate. The fifth patient (J. D.) experienced nausea, flatulence and slight epigastric burning; this patient voluntarily re-

duced his dose to one tablet three times a day. In no instance were the side effects of such a disagreeable nature that dioxyline phosphate had to be discontinued.

Of considerable interest is the fact that 6 of the 12 patients had various complaints while on placebos. These consisted of nausea, nocturia, frequency, constipation, a feeling of gaseous distention, difficulty in urination, and a metallic taste. In one instance (J. D.) these sensations caused the patient to reduce the dose; in another case (M. M.) the patient stopped the placebos because she attributed her symptoms to the tablets.

Dosage

Ten of the 12 patients were maintained on a dose of 200 mg. of dioxyline phosphate four times daily. One patient (J. D.), because of side effects as noted above, reduced his dose to one tablet three times daily. One patient (M. M.) experienced unpleasant effects, curiously enough, while on placebo and reduced her dose to one placebo tablet three times a day. Since the attending physician did not know the identity of the tablet, he continued this dose into the second period of study. Accordingly this patient was maintained on three tablets only of dioxyline phosphate even though the latter had caused no side effects. This patient may well have been able to tolerate 800 mg. per day.

Discussion

As has been previously pointed out, the evaluation of any therapeutic agent in the treatment of angina pectoris is extremely difficult.[13–16] The frequency and severity of anginal seizures depend upon the temperature, the amount of exertion, the emotional stress to which the patient is subjected, the size and nature of his meals, and many other immeasurable factors. There is frequently spontaneous improvement in a patient's anginal seizures without any specific medication. This may be attributed to the development of collateral circulation,[17] or to the result of an acute myocardial infarct with destruction of the anoxic portion of the myocardium which had been the cause of the pain.[18]

In order to attempt to assess the value of a drug in angina pectoris the problem must be approached as objectively as possible. The patients should be observed for a control period during which no coronary vasodilator is administered with the exception of nitroglycerin. Then the patient should be given either the drug to be studied or a placebo identical in size, appearance, and taste. The identity of the tablet should not be known to the physician who is following the patient. This should eliminate any possibility of suggestion on the part of the physician.

In addition to this some objective means of study such as the exercise tolerance test or anoxemia test should be done during the control period and at the end of each subsequent period of study. We believe the exercise tolerance test is more physiologic and less hazardous than the anoxemia test.

It is well recognized that positive tests are not diagnostic of angina, since they have been reported in apparently normal subjects as well as in those with neurocirculatory asthenia.[12] On the other hand some patients with unquestionable angina do not have a positive test. Perhaps the chief value of these tests in the evaluation of a therapeutic agent in angina pectoris is to observe if there is any serial change in a given patient's record. In other words, if during the control period the patient with angina has a positive test and then at the end of the period with the active drug has a negative (or possibly a less positive) test, this suggests that the vasodilator may have produced a more effective coronary blood flow. However, if the test also becomes negative at the end of the period of placebo study the conclusions are obvious.

In the present study there were 5 of the 12 patients studied who had fewer pains while taking dioxyline phosphate than either during the control period or while taking a placebo. In only one of the cases was there any increase in exercise performance after taking dioxyline phosphate. One patient was hospitalized during the period of dioxyline phosphate medication for an episode of what appeared to be coronary

insufficiency. One might speculate that had he not been on a vasodilator, a frank myocardial infarction may have resulted. This problem obviously cannot be answered.

The low incidence of serious side reactions while taking dioxyline phosphate was a conspicuous feature of this study. In no instance were these side effects sufficiently troublesome to necessitate discontinuing the drug. This is in contrast to the toxic symptoms encountered by Gray, Riseman, and Stearns,[5] in their use of papaverine; they encountered 5 of 11 patients with either nausea or abdominal cramps to such a degree that either the drug had to be discontinued or the dosage reduced from 800 mg. to 400 mg. per day. This would seem to indicate that dioxyline phosphate in equivalent dosage causes less troublesome side effects than does papaverine.

Summary and Conclusions

1. The effect of 6,7-dimethoxy-7-(4′-ethoxy-3′ - methoxybenzyl) - 3 - methyl - isoquinoline (dioxyline phosphate) has been studied in 12 patients with angina pectoris.

2. These patients have kept a daily record of the number of their pains during a control period and during alternate periods of placebo and dioxyline phosphate medication.

3. The physician who followed the patients did not know whether they were receiving placebo or dioxyline phosphate.

4. Five of the 12 patients experienced fewer pains while taking dioxyline phosphate than during either the control period or while taking a placebo.

5. Exercise tolerance tests were done during the control period and upon completion of the period of placebo and dioxyline phosphate administration. Two patients showed improvement in the test following dioxyline phosphate.

6. The usual dose was 200 mg. four times daily.

7. Side effects were encountered in five patients but were not severe and in no instance did dioxyline phosphate have to be discontinued.

8. This study indicates that dioxyline phosphate is worthy of trial in patients with angina pectoris.

Acknowledgment

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Sympathectomy for Essential Hypertension

By EDGAR V. ALLEN, M.D.

The successful treatment of essential hypertension remains one of the most difficult problems in medicine. Approximately 18 years have elapsed since extensive sympathectomy was first performed for essential hypertension. Extensive sympathectomy occasionally produces striking decrease in blood pressure of patients with essential hypertension; in many instances it fails to decrease blood pressure or modify the course of the disease. That which is most desired are some standards for preoperative selection of patients so that only patients who will be benefited by sympathectomy will be operated on. Unfortunately this apparently cannot be accomplished. The indications for sympathectomy remain at least partially uncertain and there is no agreement among those most experienced in the field of hypertension relative to the results of operation. There also are differences of opinion about the extensiveness of sympathectomy which is advisable. This paper indicates clearly differences of opinion among those most experienced in this field and emphasizes some of the points of agreement. It seems clear that additional technics of sympathectomy cannot be devised for the treatment of essential hypertension. There seems little doubt that sympathectomy would not be performed were adequate medical treatment available. This presentation gives the opinion of internists and surgeons who are particularly interested in hypertension and its treatment.

APPROXIMATELY 18 years have elapsed since splanchnicectomy and lumbar sympathectomy were first performed for essential hypertension. During this interval surgeons have developed additional surgical technics chiefly for the purpose of removing more of the paravertebral sympathetic nervous system. The rationale for sympathectomy is the concept that the increased peripheral resistance which characterizes hypertension is mediated over the paravertebral sympathetic nerves either directly or indirectly. This is by no means a valid concept in many instances. Essential hypertension may have several causes, some wholly unrelated to the sympathetic nervous system.* Hypertension originally due to sympathetic nerve impulses eventually may be due to organic arteriolar changes. After sympathectomy, arterioles may acquire "autonomy" in increasing peripheral resistance; this is suggested by the transient reduction in blood pressure in many instances. Just as there was some enthusiasm for the results of the original operation, there have been variable degrees of optimism for operative procedures developed subsequently. It seems clear that no physician or surgeon is enthusiastic about the over-all results of sympathectomy at present; sympathectomy is not a *good* method of treating hypertension in all cases.

Why then do surgeons and internists continue to recommend sympathectomy for hypertension? The answers are several. There is no medical treatment which is good in a high percentage of cases. Even medical treatment which is reasonably effective, such as sharp restriction of intake of sodium for an indefinite period may be less desirable to a patient than operation. The results of sympathectomy are occasionally brilliant and persistent. Even when sympathectomy reduces the blood pressure for only a year or two, it seems worth

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Use of the word hypertension in this presentation refers to essential hypertension unless specifically indicated.

* Hypertension owing to pheochromocytomas, coarctation of the aorta or unilateral kidney disease may mimic essential hypertension with great exactitude.

while in many instances especially as the operative mortality is low.

The physician who has to make repeated decisions relative to the advisability of sympathectomy remembers that uncontrolled, progressive hypertension is a bad disease often resembling cancer in the morbidity and mortality which it provokes. Surgical treatment for gastric cancer is widely accepted although the incidence of five-year cures following resection for such lesions is only about 30 per cent. The same attitude seems justified when sympathectomy for hypertension is under consideration.

After Dr. Blumgart requested that I prepare this article I decided to report the opinions of other experienced internists and surgeons, as well as my own. The internists who replied to my questionnaire are, in alphabetic order, as follows: Howard B. Burchell, Rochester, Minn.; James A. Evans, Boston, Mass.; Edward S. Orgain, Durham, N. C.; Robert S. Palmer, Boston, Mass.; Robert D. Taylor, Cleveland, Ohio; Henry A. Schroeder, St. Louis, Mo.; Cyrus C. Sturgis, Ann Arbor, Mich., and Paul D. White, Boston, Mass. The surgeons who replied to my questionnaire are, in alphabetic order, as follows: W. McK. Craig, Rochester, Minn.; Loyal Davis, Chicago, Ill.; Geza de Takats, Chicago, Ill.; Keith S. Grimson, Durham, N. C.; Howard C. Naffziger, San Francisco, Calif.; James L. Poppen, Boston, Mass., and Reginald H. Smithwick, Boston, Mass.

In the letter which accompanied each questionnaire I indicated my desire for an opinion rather than for statistics and facts, for I am familiar with the difficulties of acquiring statistics and facts. Also I assured each one who answered my questionnaire that I should not link opinions concerning any question directly with names in this presentation. I express my thanks to all participants. The credit of this study is largely theirs collectively; the faults are largely mine. My comments do not indicate a feeling of omniscience, for my own uncertainties are as numerous as are the uncertainties of those who answered the questionnaire.

Questions and Summary of Answers

The questions and a summary of the opinions expressed follow.

Do You Have Wholly Reliable Information that Extensive Sympathectomy (for Example T-4 through L-2) Produces Better Results than Less Extensive Sympathectomy (for Example Infradiaphragmatic Splanchnicectomy and Lumbar Sympathectomy)?*—Five surgeons and five internists answered in the negative to this question; two surgeons and two internists answered it positively. The difference of opinion expressed in these answers is easily understood.

The question could be resolved only by a process of case matching, that is, by selection of a large group of patients who were similar in regard to age, sex, duration and severity of hypertension, the status of cardiac, renal and cerebral circulation, and the retinal changes. Alternate patients then should be operated on by perhaps one of four operative procedures which differ only in the extensiveness of sympathectomy. The results of the operations would need to be assayed carefully each year for five years. To my knowledge, no study such as this has been undertaken. A less satisfactory method of study is that of patients who have had minimal sympathectomy, followed at some remote time by extension of the sympathectomy in those instances in which the original operation did not cause persistent or marked reduction of blood pressure. In a few instances, this procedure has been employed and there is some evidence that the second operations were more beneficial than the first operations.

It is well to remember that the answers indicated in the earlier part of this section do not deny that extensive sympathectomy is more beneficial than less extensive sympathectomy; they indicate only that for 10 of the 14 who replied the evidence is not wholly reliable. My own opinion is entirely in accord with those of these 10 surgeons and internists. I believe with all of those who answered this question that removal of a substantial part of the thor-

* "T" applies to "thoracic" and the numeral which follows indicates the segment. "L" refers to "lumbar."

acic paravertebral sympathetic chain is advisable.

If the Answer to the Preceding Question Is "No," Please Express an Opinion on the Subject. — As anticipated the opinions about this varied greatly. One surgeon stated that the extensiveness of the operation made no difference so long as the sympathetic supply to the adrenal glands was divided. Another surgeon favored "minimal" sympathectomy (ninth thoracic through second lumbar segments) for certain patients and "maximal" sympathectomy (third thoracic through second lumbar segments) for others. Another surgeon stated that the best results followed sympathectomy from the eighth thoracic through the first lumbar segments and that to extend the sympathectomy proximally or distally was without benefit. Another surgeon expressed the opinion that there was no choice between the various operations unless sympathectomy was extended proximally to denervate the heart, brain, lungs and upper part of the body. One surgeon favored sympathectomy of the fourth thoracic through the second lumbar segments, yet another favored section of the ninth thoracic through the second lumbar segments. One internist stated that any kind of sympathectomy prolonged survival time in malignant hypertension only; less extensive sympathectomy relieved symptoms as well as the more extensive operation. Another internist favored sympathectomy from the seventh thoracic through the second lumbar segment; yet another favored more extensive rather than "minimal" sympathectomy. Another thought the best results were achieved by sympathectomy including the seventh thoracic through the first lumbar segments, and yet another internist thought sympathectomy as extensive as section of the fourth thoracic to second lumbar segments unnecessary.

These opinions express adequately the diverse opinions of experts about the treatment of hypertension by sympathectomy. The opinions are diverse because there have not been adequate controls such as those obtained by case matching as indicated in the preceding section. My own opinion which lacks a satisfactory factual basis is that sympathectomy for essential hypertension should include the upper lumbar segments, the splanchnic nerves and at least, the lower portion of the thoracic chains.

Do You Have a Satisfactory Method of Determining before Operation which Patients Will Have the Greatest Reduction in Blood Pressure as a Result of Sympathectomy?—Five internists and four surgeons answered in the negative to this question; none gave an affirmative answer. I add my own opinion to those who replied that there is no satisfactory method of selection. Indeed I believe this to be the major flaw in the surgical treatment of hypertension. As one internist expressed it, "If we did have a satisfactory method, it would eliminate about half the operations in my opinion."

If the Answer to the Preceding Question Is "Yes," Please Describe. If the Answer Is "No," Please Describe Your Method of Selection.—One surgeon stated that he operates only on patients who have high diastolic blood pressure which cannot be controlled with thiocyanate; he excludes hypertension of "the arteriosclerotic and plethoric groups" as well as the "menopausal type" and the "fluctuant type which occurs most commonly in young individuals." Another surgeon said that he operates on three groups of patients as follows: (1) individuals less than 40 years of age who have hypertension, group 1, with minimal organic vascular disease and casual (probably meaning "not at rest" or in the office) diastolic blood pressures of more than 100 mm. of mercury, (2) middle-aged persons with arteriosclerosis with damage in brain, retina and heart but with fair renal function provided that the diastolic blood pressure rises in spite of adequate medical treatment, and (3) patients who have rapidly progressive premalignant or early malignant hypertension with severe headaches or previous coronary occlusion. The excretion of water and concentration of urine has to conform to a normal or slightly abnormal pattern. Patients with "full blown" malignant hypertension are not acceptable for operation in his opinion. A third surgeon has concluded that the best results occur in presence of persistently elevated blood pressure with slight to rather advanced cardiovascular changes. He is not

enthusiastic about operation on patients with hypertension, group 4, and advanced cardiovascular disease although survival time is prolonged. He said that ordinarily he does not advise operation for patients with mild hypertension who do not have clinical evidence of cardiovascular disease unless they have severe headache or hypertension which cannot be controlled medically.

Another surgeon and an internist expressed the opinion that the patient should be less than 40 years of age, have labile blood pressure and good renal function. Another surgeon stated that the blood pressure should be flexible, the patients less than 45 to 50 years old and "without palpatory evidence of advanced sclerosis of radial and temporal arteries."

An internist stated that operation is advisable under three circumstances as follows: (1) when there is evidence of advancing arteriolar disease in spite of medical management, (2) when very early malignant hypertension affects a young person, and (3) when disabling symptoms do not respond to medical management. According to another internist operation is indicated for the following reasons: (1) "grade 3 or grade 4 eye grounds," (2) signs of early but "reversible" renal damage, (3) enlarged heart without congestive failure, (4) nocturnal dyspnea, (5) angina pectoris without coronary occlusion, and (6) hypertensive encephalopathy including mild cerebrovascular accidents from which the patient has recovered. He requires a fairly labile blood pressure, absence of azotemia, of severe congestive failure and of recent coronary occlusion. Another internist favored operation for the following groups (1) patients who have hypertension, group 4, without significant impairment of cardiac or kidney function, (2) those with lesser degrees of severity (group 2 or 3) who have distressing symptoms and cannot or will not follow medical treatment or for whom medical treatment does not relieve symptoms, (3) those whose retinopathy does not respond in three to six months to medical treatment, and (4) the rare patient who, himself wishes sympathectomy or whose physician wishes it because as the internist wrote, "I cannot confidently predict an unfavorable result."

Another internist wrote wisely: "Failure of good medical management in progressive hypertensive vascular disease is a prime indication for sympathectomy." He stated that he rarely recommends operation when renal function is reduced, recent injury to the brain or recent cardiac injury had occurred or severe psychoneurosis, psychosis or dipsomania is present. Another internist favored operation on patients with labile hypertension, with enlarged hearts manifesting strain, and good renal function. He stated that men needed operation more frequently than women did. Another internist said that the most nearly ideal patient for sympathectomy was between 25 and 45 years of age, who has had rapid increase in blood pressure over a period of one to three years, who has minimal retinitis and whose blood pressure, particularly the diastolic, decreases to nearly normal limits with rest or sedation. Hypertensive headache he considered to be a further indication for sympathectomy. In his opinion the patient's attitude was most important; the patient's willingness to gamble on the chance of benefit was important in selection.

It is my opinion that all the indications and contraindications for sympathectomy have not been established. As I implied previously, that which is desired is to operate only on patients who will be benefited and to refrain from operating on patients who will not be benefited. There is no method for attaining this desire and, currently, physicians will need to be satisfied with operations performed on patients who are most likely to obtain marked and sustained reduction of blood pressure. In my experience the patient who is most likely to benefit is one who is emotionally well adjusted, who is anxious to endure surgical treatment if there are reasonable prospects of benefit, whose cerebral, renal and cardiac functions are impaired little or not at all, and whose blood pressure has been progressively elevated, yet still approaches normal as a result of rest or sedation. It is true that a substantial percentage of such patients will have only transient benefit and occasional patients with more hypertensive disease will be more benefited.

Do You Reserve Sympathectomy for Patients in a Certain Age Group? Please Explain.—A

surgeon answered that younger patients get better results than older ones; the arbitrary upper limit of age for women should be 50 years and for men 45 years. Another surgeon replied: "seldom over 50—none over 55." Another surgeon knew of no logical age limitation; he stated that "arteriosclerotics" should be excluded. Another surgeon wrote "below 40 ideal" and another "seldom over 50." Still another surgeon wrote that only 10 per cent of his patients were more than 50 years of age. An internist wrote, as a rule less than 40 to 45 years of age, "but some in late 40's or early 50's." Another internist stated that, in general, patients should be less than 52 years old. A third internist wrote, "don't like to do it after 50—our oldest patient 59—excellent result—chronological age less important than age of tissues." A fourth wrote that his youngest patient was 12 years of age and that operation was inadvisable for patients more than 60 years of age. A fifth wrote as follows: "rarely operate over 55—try to make distinction between chronological age and pathological age." Two internists favored patients less than 50 years old and of these one stated that patients less than 40 years of age were benefited most.

Actually, I believe a relationship between age and results has not been proved. I believe that no data are available to provide a factual answer concerning relationship of age to results. I know of no evidence to indicate that a patient 70 years old might not derive as much benefit from the operation as a patient 40 years old. Restriction of operations to patients in younger age groups may provide more five-year or ten-year survivals as the hypertension may be the only medical problem which may be troubling them or will be troublesome for some time, whereas older patients are more likely to succumb to some other disease within a short time. However, the absurdity of restriction to younger patients becomes evident if the same restriction is applied to carcinoma. Also, older patients are more likely to have benign hypertension but this is by no means uniform as their hypertension may be severe and progressive and constitute adequate reason for sympathectomy. Finally, older patients are more likely to have atherosclerosis, but no one has demonstrated that this prevents a good result from sympathectomy. It is my opinion that until conclusive evidence is obtained that older patients benefit less than younger patients, sympathectomy might be performed on some of those in the sixth, seventh and perhaps eighth decades of life, when their condition is otherwise satisfactory.

*Do You Believe that, Ideally, All Patients Should Have a Trial of Medical Treatment before Sympathectomy Is Performed?**—Four surgeons answered this question in the affirmative but two mentioned the danger of delay of surgical treatment if medical treatment is ineffective. One surgeon replied in the affirmative but excepted malignant hypertension. One surgeon answered with a firm negative. He stated that only patients with very mild or far-advanced hypertension should have medical treatment and that he knew of no evidence that medical treatment has significantly prolonged life expectancy. An internist stated that medical treatment should not be prolonged more than 6 to 12 months unless the results are good. Two other internists agreed with this opinion but excepted malignant hypertension for which they considered operation advisable. A fourth internist expressed the opinion that there is no medical treatment except the rice diet and low sodium intake which is of value in any case except cases of very mild hypertension, and he considered the rice diet and low sodium intake effective in a few cases. One internist answered yes categorically. Another wrote, "not necessarily"; he considered that patients with retinopathy with or without edema of the optic disks should be operated on provided that the surgical risk is not high. Another internist answered yes but stated that medical treatment was frequently inadequate because of poor cooperation.

It is my opinion that, ideally, medical treatment should be given a trial before a decision is made relative to sympathectomy. However, I am aware that many patients have been treated "medically" without benefit and have

* The questionnaires were answered in March and April of 1951. Since that time there have been new methods of medical treatment which might cause modification of these and subsequent answers.

succumbed to the consequences of sustained hypertension. Many of these could have been benefited by sympathectomy if it had been carried out early in the course of hypertension. Also medical treatment is frequently impossible. A salesman who eats most of his meals away from home cannot follow a program of restricted ingestion of sodium. A patient whose physician does not have adequate laboratory facilities cannot be treated adequately with potassium thiocyanate. Some medicines may gradually lose effectiveness or cause untoward symptoms. My conclusion is that patients considered satisfactory for sympathectomy should be treated medically provided that adequate medical care can be obtained. If there is no benefit in three to six months, sympathectomy should be recommended provided the hypertensive disease is not so great that sympathectomy would almost certainly fail to benefit the patient.

TABLE 1.—*The Percentage of Patients Having Normal Blood Pressure at Variable Periods after Sympathectomy*

	Per cent of patients with normal blood pressure, years after operation			
	1	2	5	10
Surgeon.....	None			
Surgeon.....	1			
Internist.....	10-15			
Internist.....	15	10		8
Internist.....			less than 10	
Internist.....	20	10	5	0.5
Internist.....	20	15	10	

What Percentage of Patients Has Normal Blood Pressure at the End of One Year, Two Years, Five Years, and Ten Years after Sympathectomy?—The few specific answers are given in table 1.

Of those who did not answer this question specifically one surgeon stated that of 124 patients who had had extensive sympathectomy in a five-year period about 50 per cent had normal blood pressure or blood pressure ranging within normal limits. Another surgeon considered that very few patients had normal blood pressure following operation. A third wrote that patients with hypertension, group 1, maintain a diastolic blood pressure between 90 and 100 mm. of mercury "in 80 per cent of cases"; and with hypertension, groups 2 and 3, "there is not a single case of normal blood pressure unless myocardial insufficiency caused it." An internist replied, "a fair number at one year—rare at ten years." Two internists wrote that they did not have figures. One surgeon wrote that a third of patients had blood pressures of less than 150 mm. of mercury systolic and 90 diastolic and that there was no recurrence of hypertension as the years passed postoperatively. My own comment is reserved until the next question has been considered.

What Percentage of Patients who Have Had Sympathectomy for Essential Hypertension Has Significant Reduction in Blood Pressure at the End of One Year, Two Years, Five Years and Ten Years?—Three internists and two surgeons did not answer this question. The opinions of those who answered specifically are recorded in table 2. Of those who did not answer specifically one surgeon stated that of patients with hypertension, group 2, 60 per cent have significant reduction of blood pressure at the end of five years; the figure for patients with hypertension, group 3, was 20 per cent. Another surgeon replied that 64 per cent had significant reduction of blood pressure at the end of four years. Another surgeon replied that 60 per cent of patients had significant reduction of blood pressure at the end of one year and 40 per cent of the living patients* four to nine years after operation.

An internist wrote only that 50 per cent of patients have material reduction of blood pressure.

The answers to the two preceding questions indicate a chaotic state of affairs which is lamentable. I could not have answered these questions with anything more satisfactory than a guess which seems to have been the method of many of those who did answer. I could make no correlation between the type of operation and the results reported by the observers, except that "total" sympathectomy was reported

* This is not the percentage of patients operated on. The surgeon indicated clearly that these figures resulted in part from many deaths.

to give good results in the highest percentage of instances. The variations and discrepancies appear to have two bases: (1) failure to agree on what constitutes normal blood pressure and significant reduction of blood pressure, and (2) failure of adequate follow-up study. It is my hope that this report will help to stimulate such studies and more factual observation in the postoperative periods. Sympathectomy has been performed for a sufficiently long period to permit better evaluation than has been carried out generally.

Do You Advise Sympathectomy for Patients without Other Complications who Have One of the Following: Papilledema, Azotemia, Angina Pectoris, Congestive Heart Failure, Myocardial Infarction or Cerebrovascular Accident?—The answers are presented in table 3.

TABLE 2.—*The Percentage of Patients Having Significant Reduction of Blood Pressure at Variable Periods after Sympathectomy*

	Per cent of patients having reduced blood pressure, years after operation			
	1	2	5	10
Surgeon....	66	66	66	66
Surgeon....	None			
Internist...	Most	Many	Few	Rarely
Internist...	75	50	50	
Internist...	65	30	5	1
Internist...	22	18	15	12

In my opinion papilledema, mild angina pectoris, mild compensated congestive heart failure and cerebrovascular accident with complete or almost complete recovery are not contraindications to sympathectomy. I have had inadequate experience with sympathectomy for moderate to severe congestive heart failure to permit an authoritative opinion. I was surprised that optimism was expressed about this situation. I agree that azotemia is a contraindication to sympathectomy. I have previously considered cerebrovascular accident without recovery to be a contraindication but I have no factual information about this or about severe angina pectoris.

What Type of Sympathectomy Do You Recommend?—Most of those who answered specifically favored splanchnicectomy; those who did not specifically mention splanchnicectomy probably took that surgical procedure for granted. In addition removal of the paravertebral sympathetic chains was recommended as indicated by various surgeons as follows: ninth thoracic through second lumbar or third thoracic through second lumbar depending on the type of case; fourth thoracic through fourth lumbar; ninth thoracic through second lumbar; "up to where major splanchnic nerve joins the paravertebral trunk," fourth, fifth or sixth thoracic—usually eighth thoracic—through first lumbar; sixth to eighth thoracic through first lumbar, and total thoracic and partial to total lumbar; celiac ganglionectomy. A surgeon and internist replied, "usually eighth thoracic through first lumbar segments; in coronary heart disease with angina pectoris from third through twelfth thoracic chains, and in certain forms of tachycardia second through twelfth thoracic." Internists stated variously: eighth thoracic

TABLE 3.—*Replies to Question, Do You Advise Sympathectomy for Patients with Certain Complications?*

Complication	Surgeons* answering:		Internists* answering:	
	Yes	No	Yes	No
Papilledema	7	0	8	0
Mild azotemia (blood urea about 60 mg. per 100 cc.)	1	5	0	8
Moderate azotemia (blood urea about 100 mg. per 100 cc.)	0	6	0	8
Severe azotemia (blood urea 200 mg. per 100 cc.)	0	6	0	8
Mild angina pectoris	7	0	7	1
Severe angina pectoris	3	4	2	4
Mild congestive heart failure (compensated)	6	1	8	0
Moderate congestive heart failure	2	5	2	6
Severe congestive heart failure	1	6	2	6
Acute myocardial infarction less than 1 year previously	3	4	4	3
Acute myocardial infarction more than 2 years previously	4	3	5	3
Cerebrovascular accident with complete or almost complete recovery	7	0	7	1
Cerebrovascular accident without recovery	1	6	2	6

* Not all replied on all points.

through first lumbar paravertebral sympathetic chains; seventh thoracic through first lumbar; eighth thoracic through second lumbar; first thoracic through first lumbar and "let the surgeon decide—I favor more extensive sympathectomy"; fourth or fifth thoracic through second lumbar (third lumbar in women).

These answers show no agreement except that splanchnicectomy alone is inadvisable. There was wide disagreement on the extensiveness of removal of the paravertebral chains which was considered advisable. Unfortunately, there is little tangible evidence which favors the effectiveness of one type of operation over another. It is unfortunate, indeed, that there have been inadequate controls but the problem of controls, as indicated previously, requires a system of case matching which is extremely difficult.

Do You Believe that Sympathectomy Is Advisable for the Relief of Headache even when the Prospects of Reducing the Blood Pressure Are Very Minimal?—Two surgeons answered with an affirmative. Three answered with "yes" provided that headache was disabling or not amenable to medical treatment and one answered "yes" provided that the patient understood the operation was palliative only. One surgeon answered "no." Two internists answered "no" and three answered "yes." Two other internists answered "yes" provided that headache was disabling and not amenable to medical treatment.

Hypertensive headache is seldom indeed disabling or cannot be relieved by medication, such as with potassium thiocyanate. It is my belief that severe hypertensive headache alone is seldom if ever an indication for sympathectomy. If there are very minimal prospects of reducing blood pressure because of advanced complications of hypertension, and headache is refractory to medical treatment of the hypertension, I favor the use of opiates or allied drugs. If there is reasonable prospect of reducing the blood pressure by sympathectomy this in itself should be adequate reason for sympathectomy; headache will almost certainly be relieved.

Do You Have Definite Evidence that Sympathectomy Increases Survival Time of Patients with Hypertension?—Seven surgeons answered "yes" to this question; one qualified his answer by the words "in malignant hypertension." One surgeon who answered "yes" expressed the view that mortality rates are reduced by sympathectomy even if the blood pressure is not reduced. Two internists answered "no"; one said that the evidence was acceptable and four answered "yes." I believe the evidence is wholly acceptable that reduction of blood pressure as a result of sympathectomy (or by any other means) increases survival time. I do not believe the evidence is wholly acceptable that sympathectomy increases survival time when the blood pressure is not reduced.

Do You Believe That Sympathectomy Produces as Good Results as the Best Medical Treatment? Better Results?—Two internists considered surgical treatment as good as the best medical treatment; an additional internist qualified his answer by saying "in many cases." One internist stated surgical treatment is better than medical treatment and one qualified his answer by the words "in many cases." A sixth internist wrote that surgical treatment was as good as medical treatment in some cases and better in others. The seventh wrote that the results of surgical treatment were better in a larger percentage of cases and the eighth replied that the question was unfair; if the results of medical treatment were good, the results of surgical treatment were not better. One surgeon stated that surgical treatment was better than medical treatment; one qualified his answer by the words "in many cases." A third had found that the results were as good in some cases and not as good in others. Another considered that the results of sympathectomy were better in cases of retinopathy, early renal damage, enlarged hearts without congestive failure and mild encephalopathy. A fifth was uncertain and another indicated that the results were better if patients did not respond to medical treatment. The seventh wrote that sympathectomy was inadvisable except for a certain group of patients who cannot be managed medically; all others should have medical treatment.

As an internist I find with others that medical treatment of hypertension is frequently entirely unsatisfactory at the time patients first

come to me for examination. This I believe to be the true indication for sympathectomy provided there are no contraindications. In all probability, this would not be the usual situation if patients presented themselves for examination at a much earlier period in the development of their hypertension. Unfortunately some surgeons recognize little benefit from any medical treatment just as some internists take a dim view of the value of surgical treatment. These opinions are largely the result of a one-sided approach to the problem; there is benefit from surgical treatment in many cases and from medical treatment in many cases. One great virtue of sympathectomy is its expeditiousness; in many instances it is preferable to medical treatment which must be continued indefinitely.

How Often Is Pain a Major Problem after Sympathectomy for Essential Hypertension?—One surgeon answered "never"; another answered "occasionally for a few months"; another answered "infrequently"; a fourth wrote "of minor consequence" and another "rarely, my guess is 1 per cent." Another surgeon had noted pain in 13 per cent of cases; it endured not longer than six months. One internist answered "very rarely" and another wrote "almost always" for six weeks to two to three years. Another internist considered pain a constant but variable problem; it disappeared in most instances within three months but might continue for six to twelve months. A fourth internist answered in 25 to 30 per cent and another said in 20 per cent for periods up to three months. One internist wrote "almost always"; another wrote "rarely" and another "in a small per cent for two months."

Neuralgia following sympathectomy may be a most painful condition, distressing to patient and physician alike. Fortunately it is rarely severe and usually disappears promptly. The noted incidence of it will be sharply increased by routine questioning and recording; this probably accounts for the discrepancy in the answers reported although surgical technic may be a factor. The possibility of neuralgia should never constitute a reason for failure to recommend sympathectomy although it seems wise to inform patients that it might occur.

How Often Is Orthostatic Hypotension a Serious Problem after Sympathectomy?—Five internists and three surgeons answered "seldom," "rarely," "not a serious problem" or "practically never." One internist replied "very often" and another "for three to six months when operation is successful." One internist and two surgeons stated that orthostatic hypotension was troublesome for most patients for periods up to three months. Another surgeon replied "in 10 per cent."

Orthostatic hypotension occurs almost routinely after sympathectomy. In a few instances the blood pressure is so low when patients stand that there is danger of syncope. Fortunately this can be prevented if both legs are wrapped snugly with an elastic bandage and an abdominal binder is worn; both bandage and binder can be discarded within a few weeks. Orthostatic hypotension of lesser degree may persist for many months; in many instances it is the only tangible evidence of benefit from sympathectomy. The disappearance of orthostatic hypotension remains without satisfactory explanation; there is some reason to believe that the arterioles and venules have acquired autonomy, an early manifestation of loss of benefit from sympathectomy.

Do You Shy Away from Recommending Sympathectomy for Hypertension for Patients who, in Addition, Have Anxiety Tension States (Psychoneurosis) Manifested by Nervousness, Weakness, Insomnia, Overt Anxiety and Other Somatic Complaints?—Five surgeons replied "yes" but of these two indicated that the emotional situation might be improved before operation or sometimes benefited by operation. One surgeon replied with an emphatic "no" indicating that operation improves the general condition in many instances. Four internists replied "yes" but one qualified his answer by the observation that simple tension states may be benefited and another by the observation that psychiatric care might improve the situation sufficiently to permit sympathectomy. Three internists answered "no." My own answer to this question is "yes." I am aware that sympathectomy frequently lessens manifestations of nervous tension. However, it has always seemed unwise to me to operate on patients for

hypertension when the major part of their ill health stems from an emotional disturbance. I have noted that some patients with conditions mentioned in the question have prolonged periods of recovery from operation or indeed continue in ill health. Certainly I would not recommend sympathectomy for such patients without capable psychiatric evaluation.

Do You Believe that Active Duodenal Ulcer Is a Contraindication to Sympathectomy for Hypertension?—One surgeon and three internists replied "yes" to this question. Two internists stated that the ulcer should be treated and "under control" before sympathectomy. One internist replied "no" as did two surgeons in whose experience the ulcer gave no additional difficulty after sympathectomy. Two surgeons recommended vagotomy at the time of the second sympathectomy; of these one stated that sympathectomy, vagotomy and gastroenterostomy might be advisable.

If You Had a Patient with Unilateral Renal Disease (Urologic Examination) and Normal or Slightly Elevated Blood Urea, which of the Following Would You Recommend: Nephrectomy, Sympathectomy, or Both?—The answers follow: Four internists and three surgeons favored nephrectomy provided that blood urea is normal and the diseased kidney markedly reduced in function or size. Two internists and three surgeons favored nephrectomy and sympathectomy and if the blood pressure is not reduced by this operation, sympathectomy on the other side. Two internists favored sympathectomy.

The problem presented by this situation is chiefly one of gaining information. If the surgeon performs both sympathectomy and nephrectomy and the blood pressure is sharply reduced, he can never be certain whether nephrectomy or sympathectomy produced the good results although unilateral sympathectomy alone is seldom beneficial. I am frequently puzzled as to the best procedure for the patient. If, on the basis of prior experience it seems most likely that the hypertension is renal in origin, nephrectomy alone is advisable. If the blood pressure remains high, bilateral sympathectomy is then recommended. If it seems unlikely although possible that the hypertension is renal in origin, sympathectomy and nephrectomy may be performed at the same operative session, followed by sympathectomy on the other side if the blood pressure remains high.

Comment

This study has disclosed many views and opinions and that there are disagreements about many aspects which can be resolved only by a careful plan of case matching. It seems unlikely that careful case matching will be accomplished in the future, however desirable it may be.

There is no doubt but that many patients are benefited by sympathectomy. Unfortunately no method or methods are known by which proper selection can be made in order that only those patients who will be benefited will be operated on. It is agreed that azotemia is a contraindication to sympathectomy and it seems likely that patients who have other advanced complications of hypertension respond less well than those who have compensated hypertension. It is unfortunate that many patients receive no treatment or inadequate treatment with the result that hypertension has progressed so much that no kind of treatment will reduce blood pressure. Physicians should not carry on "medical treatment" (often meaning no treatment) which gives little or no benefit until the golden period in which sympathectomy might be of benefit, has passed. It is probable that no additional technics of sympathectomy will produce better results than those currently in use. It is logical to believe that if any further contributions are made for the solution of the problem of essential hypertension, they will be medical measures. Until that time, patients who have a reasonable prospect of benefiting from sympathectomy should not be denied this surgical procedure, particularly if a short period of medical treatment does not cause satisfactory reduction of blood pressure and contraindications do not exist.

ABSTRACTS

BACTERIAL ENDOCARDITIS

Friedberg, C. K., and Bader, M. E.: Acute Staphylococcic Endocarditis Cured with the Aid of Bacitracin. J.A.M.A. **147:** 46 (Sept. 1), 1951.

The authors report the first case of acute *Staphylococcus aureus* endocarditis in which cure followed the parenteral use of bacitracin in conjunction with other antibiotics. Bacitracin appeared to be effective after the disease had not been controlled by huge doses (over a period of 12 days) of penicillin, Aureomycin, and chloramphenicol. No significant toxicity was associated with the administration of bacitracin. Because of the increasing frequency of penicillin-resistant strains of *Staph. aureus*, the availability of bacitracin as another potent antibiotic in serious staphylococcic bacteremias and endocarditis is noteworthy.

KITCHELL

BLOOD COAGULATION

Mann, F. D., Hurn, M., and Barker, N. W.: Platelets and the Coagulation Defect Caused by Dicumarol. Am. J. Clin. Path. **21:** 814 (Sept.), 1951.

The authors tested the theory propounded by them that the change in the clotting mechanism caused by Dicumarol consisted in large part of a deficiency in a substance which acted upon thromboplastin before prothrombin and its other conversion factors entered into the reaction. They attempted to determine whether this substance, which they called cothromboplastin, affected thromboplastin of platelet origin as it did tissue thromboplastin.

It was found that relatively more serum or cothromboplastin was required to act on platelets than on tissue extracts, and the resulting activity was much less. However, the platelet material, whether from normal or from dicumarolized persons, appeared to function in a manner analogous to tissue thromboplastin, and it was affected in the same way by the cothromboplastin reaction.

It was believed that whether the coagulation process was initiated by injured or by injured platelets, it was similarly affected by dicumarol.

ABRAMSON

Kaplan, S. H., and Friedman, I. A.: Effects of Ultraviolet-Ray Irradiation on Clotting Mechanism of Plasma. J.A.M.A. **147:** 229 (Sept. 15), 1951.

Because of reported alterations in the clotting mechanism of irradiated plasma (irradiated with ultraviolet-rays of 1,849 Å) the authors decided to make a careful study to determine whether or not it had any anticoagulant properties. They felt that the previous reports were in error because these reports did not consider the age of the plasma and the fact that it contained sodium citrate. It has been shown that after three months, prothrombin concentration in liquid plasma is 17 per cent of normal with an intact fibrinogen content. By the end of six months, the prothrombin level is down to 2 per cent and the fibrinogen has completely disappeared. After careful studies, the authors conclude that ultraviolet-ray irradiation of fresh plasma does not alter its clotting mechanism. The inability of aged liquid plasma whether iradiated or not to clot upon the addition of thrombin is due to the disappearance of fibrinogen and the process can be reversed by the addition of this substance. The inhibition of in vitro clotting of fresh blood by the addition of plasma is due to the sodium citrate in the plasma. Administration of aged irradiated liquid plasma in 600 cc. quan-

tities has no effect on the clotting mechanism of recipients.

KITCHELL

Overman, R. S., and Wright, I. S.: Prothrombin Time Determinations on Patients with Myocardial Infarction. J.A.M.A. **147:** 227 (Sept. 15), 1951.

It has long been felt that there is an increased tendency towards blood coagulation in the presence of coronary thrombosis. Previous studies have yielded evidence that hyperprothrombinemia is one of the factors responsible. The authors studied the data on 12.5 per cent diluted plasma prothrombin times on 17 patients with myocardial infarction and on 25 normal persons. They found that the group with myocardial infarction showed a mean prothrombin time of 32.29 seconds and the mean of the normal group was 38.6 seconds. This difference is statistically highly significant. The study does not in any way, however, reveal the reason for the observed difference.

KITCHELL

Rotter, R., and Meyer, O.: Clinical Evaluation of 4-Hydroxycoumarin Anticoagulant No. 63. Arch. Int. Med. **88:** 296 (Sept.), 1951.

The 4-hydroxycoumarin anticoagulant No. 63 is a safe and effective preparation for use in treatment of thrombo-embolic disorders. The advantages of this substance over bishydroxycoumarin (Dicumarol) are the earlier appearance of therapeutic prothrombin levels and the ease of maintenance of these values with a fixed dose of the anticoagulant.

Toxic side effects of compound No. 63 are minimal and the incidence of microscopic hematuria is less than half that which occurs after use of bishydroxycoumarin. Experience so far shows the best antidotes for the hypoprothrombinemia induced by this anticoagulant are vitamin K_1 and, possibly, vitamin K_1 oxide. Blood transfusions and administration of water-soluble vitamin K preparations were far from being efficacious in most instances.

BERNSTEIN

Svihla, A., Bowman, H. R., and Ritenour, R.: Prolongation of Clotting Time in Dormant Estivating Mammals. Science **114:** 298 (Sept. 21), 1951.

The authors found a prolongation of blood-clotting time in a group of ground squirrels, by three standard technics. The clotting time averaged twice as long in dormant animals by the Lee and White method than in the active animal, and was increased five times by the capillary tube method.

During estivation, the heart beats slowly with a comparable decrease in rate of blood flow and hence the prolongation of clotting time is a remarkable adaptation to the dormant state. The danger of thrombus formation is considerably reduced while the possibility of traumatic bleeding is unlikely during estivation.

WAIFE

Reid, Robert A.: Treatment of Hypoprothrombinemia with Orally Administered Vitamin K_1. Quart. Bull. Northwestern Univ. M. School **25:** 292 (Fall), 1951.

The author administered vitamin K_1 to nine patients with hypoprothrombinemia. Seven of these patients were bleeding, with manifestations ranging from gross hematuria to bleeding from all orifices. Dicumarol administration accounted for eight of the cases, and one patient developed hypoprothrombinemia from the self-administration of 8 to 10 aspirin tablets a day for about a month.

The oral administration of single doses of vitamin K_1 (333 mg. to 1000 mg.) in all cases resulted in an increase in the prothrombin percentage to normal within 16 hours. More important than this laboratory evidence of return to normal is the fact that bleeding ceased in all cases.

BERNSTEIN

Soulier, J. P., and le Bolloch, A. G.: The "in Vitro" Heparin Tolerance Test in the Control of Dicumarol Therapy. Acta med. scandinav. **140:** 132 1951.

The authors express the opinion that the control of Dicumarol therapy by means of determination of the prothrombin level alone is inadequate. They point out that although Dicumarol therapy has a constant effect upon the prothrombin, the resultant hypocoagulability is variable. If there is a deficiency of some clotting agent, such as a thrombocytopenia, a more pronounced hypocoagulability than desired may result, whereas if an excess of clotting factors is present, such as thromboplastin or Ac globulin, a satisfactory hypocoagulability will not be produced in spite of a severe hypoprothrombinemia. They consider the combined use of the Quick prothrombin time and a modification of the Waugh and Ruddick "in vitro" heparin tolerance test upon the same oxalated plasma perfectly suited for determining the over-all coagulability of the blood. Once an efficient level of prothrombin is determined, it is no longer necessary to repeat the heparin tolerance test each time. The authors express the opinion that when a prothrombin level of 10 per cent with Dicumarol is not sufficient to obtain hypocoagulability, it is better to change to heparin.

ROSENBAUM

Hartman, R. C.: The Thrombin-inhibitory Effect of Certain Thromboplastin Preparations. Am. J. M. Sc. **222:** 279 (Sept.), 1951.

The author studied the retarding action of several thromboplastin preparations upon the rate of conversion of fibrinogen to fibrin by thrombin. The

thrombin-inhibitory effect was noted in thrombin-fibrinogen mixtures as well as in the Quick one-stage prothrombin time test using human plasma. When higher concentrations of thrombin solutions were employed, the inhibitory effect of thromboplastin was not observed. Other factors which influence the rate of thrombin-fibrinogen reaction such as pH, calcium ion concentration and the presence of oxalate ions were studied and found not to be involved in the retarding effect noted. Protamine titrations were employed to exclude heparin as the cause of the antithrombin action of the thromboplastin preparations. A sedimentable material obtained from thromboplastin suspensions was free of thrombin-inhibiting effect and remained potently thromboplastic suggesting that another substance is present which is responsible for thrombin inhibition. It is suggested that this factor may provide an explanation for discrepancies noted in prothrombin estimations using various thromboplastin preparations.

SHUMAN

CONGENITAL ANOMALIES

Sheedy, J. A., Gottstein, W. K., and Fenn, G. K.: Cardiac Failure After Aortic-Pulmonary Anastamosis in Tetralogy of Fallot. Am. J. Med. **11:** 403 (Sept.), 1951.

In this report the authors describe the fatal course of events following an aortic-pulmonary arterial anastamosis performed in a 31 year old male who demonstrated the tetralogy of Fallot and an interauricular septal defect. The postoperative course was complicated by pleural effusion, pericarditis, azotemia, anemia, and jaundice. The latter was attributed to chronic passive congestion although viral hepatitis could not definitely be excluded. Death from progressive congestive failure occurred three months after the operation. The authors believe that the auricular septal defect and the increased work loss imposed by the artificial patent ductus may have exhausted the remaining cardiac reserve despite the improvement in anoxia following the operation.

HARRIS

Clagett, O. T., and Jampolis, R. W.: Coarctation of the Aorta: A Study of Seventy Cases in which Surgical Exploration Was Performed. Arch. Surg. **63:** 337 (Sept.), 1951.

The authors review their experience with 70 cases of coarctation of the aorta in which surgical exploration was performed at the Mayo Clinic.

The average age of these patients was 24½ years—the youngest was 7 and the oldest was 50. They believe the optimum time for operative intervention to be between 15 and 20 years of age.

Of the 70 patients explored, eight could not be resected. There were five operative deaths in the 70 patients, a mortality rate of 7.1 per cent. In the last 55 cases, exploration has been performed without a death. Postoperative complications were minimal. The five deaths were due either to heart failure or to postoperative hemorrhage.

Because of the poor long term survival rate of patients with coarctation of the aorta, an attempt should be made to correct the defect by surgical means regardless of age, myocardial conduction defects, previous cerebrovascular accidents, or previous congestive failure.

FROBESE

Halonen, P. I., Heikel, P. E. and Maganen, P.: Constitutional Changes in Patients with Coarctation of the Aorta. Cardiologia **18:** 321, 1951.

The authors studied 28 cases with coarctation of the aorta for the presence of other constitutional anomalies. Systematic attention was paid to the following details: Type of skull, size and length of the neck, presence of skin folds, level of the hairy scalp, position of the ears, distribution of the body hair, deformities of the bones, intelligence and sexual development.

All cases had a platycephalic skull, 20 subjects were brachycephalic. There was a high incidence of bone deformities in the upper part of the body and of anomalies in the position of the ears and the hair line. One instance of Klippel-Feil syndrome and another of Turner's syndrome were found among the material. The authors feel that the coarctation of the aorta and other constitutional anomalies, as encountered in these studies, may be manifestations of the same developmental disturbance.

PICK

CONGESTIVE HEART FAILURE

Bergner, G. E., Hutchinson, J. H., Koehler, J. W., and Czebrinski, E. L.: Metabolic Problems Arising in The Management of Congestive Heart Failure. Arch. Int. Med. **88:** 387 (Sept.), 1951.

The electrolyte patterns of 24 patients with cardiac disease were studied before and after treatment with ammonium chloride and mercurial diuretics. In 16 of these patients serum pH studies were also made. Varying degrees of acidosis were observed, and one case of salt depletion was noted. Anorexia and drowsiness were valuable clinical signs that electrolyte imbalances were developing.

The observations recorded demonstrated that the therapeutic measures used to correct cardiac decompensation may have a profound influence on salt, water, and nitrogen metabolism of the body, as well as on the acid-base balance. The several patients in this report in whom ammonium chloride acidosis developed presented a fairly typical electrolyte pattern. The chloride level was always high, and the carbon-dioxide-combining power and the serum pH were low. A few also showed a lowering of the sodium

level. Serum potassium was usually increased but not in proportion to the rise of the urea nitrogen. With the correction of the acidosis, all elements except the potassium tended to return promptly to normal values. During the rehydration of the patient with the severest acidosis, the serum potassium showed a drop to subnormal values, a situation similar to that seen during the correction of diabetic acidosis. The intermittent use of ammonium chloride prevented severe acidosis but allowed satisfactory diuresis.

BERNSTEIN

Feldman, D. J.: Localized Interlobar Pleural Effusion in Heart Failure. J.A.M.A. **146:** 1408 (Aug. 11), 1951.

Localized interlobar pleural effusion has been recognized frequently since the first report by Stewart in 1928. Such effusions are characterized by their reversibility, appearing during congestive heart failure and clearing rapidly when the failure responds to treatment or disappears spontaneously. Having once appeared as a feature of heart failure, they tend to recur with subsequent episodes. Such a case is reported by the author who discusses the problem presented by them and the importance of their differentiation from intrinsic pulmonary lesions, particularly neoplasm. The available literature is reviewed.

KITCHELL

CORONARY ARTERY DISEASE, MYOCARDIAL INFARCTION

Doret, J. P., and Ferrero, C.: Inequality of Skin Temperature in Myocardial Infarction and Angina Pectoris. Cardiologia **19:** 80 (fasc. 1), 1951.

In the majority of cases with myocardial infarction and angina pectoris the author found a low skin temperature involving thorax, shoulder and upper extremity, at the site of the pain radiation, which he ascribed to reflect vasoconstriction in these regions. In recent infarcts with rapidly subsiding pain and benign course, this relative hypothermia disappears within four to seven weeks in contrast to cases where pain attacks continue after the acute episode. This would suggest that anginal pain, persisting or recurring after myocardial infarction, is vasomotor in origin. Localized hypothermia is also found frequently in spontaneous and provoked attacks of effort angina and is most marked in the regions of maximal pain radiation. There is, however, no relationship between decrease of skin temperature and local hyperesthesia. Variations in the localization of the hypothermic zones were not dependent on the electrocardiographic localization of the myocardial infarct.

PICK

Botelho Reis, N., and Amorim, E.: The Roentgenologic Diagnosis and Clinical Importance of Coronary Artery Calcification. Arq. grasie. cardiol. **4:** 293 (Sept.), 1951.

Following a brief review of the available literature, the authors emphasize the need of a thorough knowledge of the anatomic and roentgenologic aspects of the coronary arteries in order to diagnose calcification of these vessels. The observer must be aware of the various reontgenologic features such as the double line of calcification and the rosary-shaped and nodular aspects, in addition to the motility of the coronary arteries and the various types of cardiac and extracardiac calcifications with which they may be confused. The great advantages of fluoroscopy are noted, particularly with certain types of screens, which enable the observer to diagnose even slight degrees of coronary calcification often misdiagnosed roentgenographically.

Four cases are reported, in which these methods were compared. In two cases, there was a marked degree of calcification of both coronary arteries, whereas in the remaining two patients the left coronary artery was solely involved and diagnosed on routine fluoroscopy. In three cases, there was a history of myocardial infarction and one patient, in whom the electrocardiogram was inconclusive, suffered from angina pectoris.

It is the authors' belief that the routine search for coronary calcifications in all patients over 50 years of age, particularly in those with a history of coronary insufficiency, would materially increase the incidence of this roentgenologic diagnosis.

SCHLESINGER

Zoll, P. M., Wessler, S., and Blumgart, H. L.: Angina pectoris. Am. J. Med. **11:** 331 (Sept.), 1951.

A clinico-pathologic study of angina pectoris was carried out by the authors in a group of 848 cases in which the coronary arteries were injected and dissected by the Schlesinger technic. Of this group, 671 patients without cardiac pain were controls. All 177 patients with angina pectoris of one month's duration or longer had either coronary, valvular, or hypertensive heart disease. Coronary narrowing or occlusion was found in 90 per cent of these patients. Angina occurred in 52 per cent of the patients with coronary occlusion, in 16 per cent of patients with valvular heart disease, in 5 per cent of patients with coronary narrowing, and in 3 per cent of patients with hypertension.

The author found that the average duration of angina pectoris differed according to the underlying etiology, being shorter in valvular heart disease and longer in coronary heart disease. One-third of the patients died one year after the onset of angina; one-half were dead within two years; three-quarters died within five years and nine-tenths died within 10 years. Congestive failure was of more serious prognostic importance than angina pectoris in coronary disease and less serious in valvular disease. An inter-

current eipsode of myocardial infarction did not shorten the prognosis of a patient with angina pectoris. In coronary artery disease, myocardial ischemia produces angina pectoris, myocardial fibrosis, and intercoronary anastomoses.

HARRIS

Levi, G., and Salvini, L.: Calcification of the Coronary Arteries. Cardiologia **19:** 260 (fasc. 4), 1951.

A 65 year old female with a two year history of retrosternal pressure on exertion revealed at x-ray examination annular calcifications encircling the heart shadow, which followed the course of the coronary arteries, from their origin in the aorta to the apex of the heart. A kymogram showed that the shadows pulsated in lateral direction and synchronously with the cardiac contractions, and a tomogram confirmed their position on the anterior and posterior surface of the heart. The electrocardiogram of the patient showed low voltage in the limb leads, and small and diphasic T waves in both limb and precordial leads.

The authors consider these data sufficient for interpretation of their observation as calcification of both coronary arteries. They exclude the possibility of pericardial calcification in view of the history of the patient, the type of the calcification and its distinct pulsations, and of the electrocardiogram, which, in their opinion, substantiates the diagnosis of coronary disease.

PICK

Drake, E. H.: Coronary Sclerosis and Pulmonary Hypertension. Ann. Int. Med. **35:** 600 (Sept.), 1951.

A physician with coronary disease complicated by three episodes of myocardial infarction, has had repeated bouts of pulmonary infarction, during each of which there was an exacerbation of his anginal symptoms. A 66 year old female with mitral stenosis and an antecedent myocardial infarct, developed an exacerbation of her anginal symptoms following an attack of pneumonia. It is therefore inferred that factors which raise the pressure in the lesser circulation will provoke or exaggerate anginal symptoms in patients with pre-existing coronary sclerosis. The therapeutic implications of this conclusion are discussed.

WENDKOS

Vedoya, R., Copello, C. E., and Nessi, C. T.: Differentiation between Real Post-Tachycardial Syndrome and Coronary Insufficiency Caused by Paroxysmal Tachycardia. Rev. argent. cardiol. **18:** 77 (March–April), 1951.

Two different electrocardiographic patterns may be observed after attacks of paroxysmal tachycardia. The first is the *real post-tachycardial pattern* which appears after ventricular tachycardia, especially in young people. It consists of deeply inverted, symmetric T waves. These are present either in lead I or lead III according to the configuration of the complex during the attack because they are closely connected with the original focus of excitation. These changes persist for about a week and reappear after every attack.

The second pattern is that of *coronary insufficiency* and is observed chiefly in older persons. These patients complain of precordial pain and present depression of S-T during the attack. These changes are observed after the attack, but disappear within a few days, and are of a shorter duration than those of the first pattern.

LUISADA

ELECTROCARDIOGRAPHY

Chiaverini, R.: Electrocardiographic Studies on Right Ventricular Strain. Arq. brasil. cardiol. **4:** 249, 1951.

The electrocardiographic patterns of total and subtotal compression of the pulmonary artery were studied by the author in a series of 20 dogs and compared with the effect of compression of the aorta in some of the experiments.

Both the effects of acute and progressive (cellophane) compression were studied.

The results of this study are the following: (1) During acute compression, when the exploring electrode was placed over the trabecular zone of the right ventricle, an increase of the R/S ratio was noted. Opposite changes were noted when the electrode was placed over the conus of the pulmonary artery. This was explained as the result of incomplete intraventricular block of the right bundle branch system, caused by the sudden increase of right ventricular pressure. (2) Primary changes of ST-T were noted. These changes are explained as the result of decreased coronary flow (increased pressure of the coronary sinus) and engorgement of the thebesian vessels. The above alterations were observed also in atropinized animals. Therefore, no pulmocoronary reflexes were involved. All the above changes took place early in the experiment. (3) With progressive compression, the first stage of right ventricular hypertrophy was accompanied by shift toward the left of the mean electrical axis, independent of the position of the heart.

LUISADA

Bellet, S., and Finkelstein, D.: Significance of the QT Prolongation in the Electrocardiogram: Based on a Study of 168 Cases. Am. J. M. Sc. **222:** 263 (Sept.), 1951.

The authors have classified the clinical states in which QT prolongation in the electrocardiogram is observed into six groups. The first group is that associated with electrolyte disturbances in which hypocalcemia and hypopotassemia or both were the principal factors. A large number of clinical disorders were found to produce these serum electrolyte

alterations. Administration of the specific electrolyte involved in the deficiency corrected the ECG abnormality for which it was responsible. The second group includes 20 cases of myocardial disease of which the largest subdivision is rheumatic myocarditis (13 cases). The third group consists of those conditions associated with myocardial anoxia. The Q-T prolongation is observed in 11 patients with myocardial infarction and 5 patients with pulmonary embolus as well as in other anoxemia states such as carbon monoxide gas poisoning and Stokes-Adams attack. The fourth group includes combined factors of anoxemia and hypopotassemia such as occurs in insulin shock therapy and in avitaminosis. The fifth group includes eight patients who manifested prolonged Q-T intervals while receiving quinidine therapy. The sixth group consists of six patients in whom no etiologic factor could be determined.

Difficulties in the measurement of the Q-T interval occur when a prominent U wave is present. The authors believe that under these circumstances the Q-T or Q-U interval may be used interchangeably to measure electrical systole because of observations reported by them indicating that, the U wave may appear as part of the T wave and, in hypopotassemia, may be altered by treatment. The use of the electrocardiogram as an aid in the diagnosis of electrolyte disturbances and as a guide in the therapeutic management of these cases is discussed.

SHUMAN

Gilmann, H.: On the Possibility of "Aimed" Additional Electrocardiographic Leads. Cardiologia **19:** 47 (Fasc. 1), 1951.

The author shows by the help of diagrams that each of the electrocardiographic leads customarily used can be visualized in form of a radius. The radii connect various points of the surface of a sphere, which represents the body surface, with its center, the heart. For each instantaneous vector, generated by the heart, there will be an optimal radius, parallel to the lead with the maximal deflection. The optimal radius, that is, the lead or leads which will show best a particular lesion, can be predicted under consideration of the direction and the mode of ventricular activation under normal and abnormal conditions. Thus, the effects of an epicardial lesion in the left ventricle can be best demonstrated in leads I, II, V_4, V_5 and CR_4 to CR_6, and those of the right ventricle are expected to become apparent in III, V_1 and CL_1 to CL_6. Other optimal combinations of leads for demonstration of recent and old infarctions of various localizations, and of right and left bundle branch lesions can be derived from the diagram presented.

The author believes that the taking of 12 lead electrocardiograms including a full set of precordial leads is not necessary for routine electrocardiography. He recommends as pertinent leads the three standard leads, V_1, V_4 and AVF, to which complementary leads may be added and "aimed" according to the suspected localization of the lesion.

PICK

Schindler, J. and Forster, R.: Electrocardiographic Findings in Dystrophia Myotonica: Dystrophia Cordis Myotonica. Cardiologia **19:** 18 (Fasc. 1), 1951.

The authors report the cardiovascular findings in 24 cases of dystrophia myotonica with special reference to alterations of the electrocardiogram. In three cases, the heart was abnormally small and in six, enlarged to the left. Low blood pressure was found in 15 cases and signs of heart failure in two. In 18 instances (75 per cent), the electrocardiogram was abnormal. The alterations consisted of disturbances in rhythm (ventricular premature beats, auricular flutter and fibrillation), prolongation of A-V and intraventricular conduction, and abnormalities of repolarization (low or inverted T waves and prolongation of the Q-T interval). None of these changes were influenced by intravenous injection of Calcium-Quinine. In one patient who died histologic examination of the heart showed severe degenerative changes of the myocardium.

The authors feel that the primary disturbance in dystrophia myotonica consists in an anatomic and functional alteration of the muscle fibers including both skeletal and heart muscle. There appears to be a predisposition in the heart for affection of this specific system by the disease, leading to the described disturbances of impulse formation and conduction.

PICK

Carouso, G., Maurice, P., Scebat, L., and Lenegre, J.: The Electrocardiogram in Right Ventricular Hypertrophy. Arch. mal. coeur **44:** 769 (Sept.), 1951.

This study is an anatomic-electrocardiographic correlation in 63 cases with pure right ventricular hypertrophy of various etiology. The method of Wilson and Hermann was used for the anatomic diagnosis and the weight quotient $\frac{\text{left ventricle}}{\text{right ventricle}}$ was less than 1.5 in all cases. Cases with hypertrophy of both ventricles were excluded.

The most common electrocardiographic signs of pure right ventricular hypertrophy are right axis deviation in the standard leads, usually associated with an abnormal R/S ratio in V_1–V_2 and V_5–V_6. Right axis deviation without changes in the precordial leads is significant only if exceeding +112 degrees. Right axis deviation of more than 120 degrees is usually associated with a prominent R wave in aV_R. A number of cases showed the pattern of incomplete or complete right bundle branch block. Histologic examination of the septum revealed lesions of the right bundle branch in part of the latter and in none of the former cases.

There appeared to be a definite relationship between the clinical cause of right ventricular hypertrophy and its electrocardiographic pattern. Thus, right axis deviation exceeding +150 degrees is seen frequently in chronic cor pulmonale and in congenital anomalies and infrequently in mitral disease. An abnormal R/S ratio involving both the right and left precordium may be seen in right ventricular hypertrophy of any type. It is restricted to V_1 mainly in mitral disease, and to V_5 and V_6 in chronic pulmonary disease. These variations of the precordial pattern were found to depend also on the degree of ventricular hypertrophy as indicated by the weight quotient of left and right ventricle. The R/S ratio was reversed in all chest leads when this quotient was 0.78 to 0.92, was abnormal in V_1 only with a quotient of 1.1, and was normal when the quotient was greater than 1.2. The size of the R wave in precordial leads of cases with right ventricular hypertrophy seems to depend on the location of the chest electrode with respect to the crista supraventricularis, the region in the right ventricle which usually shows the most marked degree of hypertrophy.

PICK

Meyer, P., and Schmidt, C.: Electrophysiologic and Clinical Significance of Precordial Tracing of the Rectilinear Type, Particularly in Left Ventricular Hypertrophy. Arch. d. mal. coeur **44:** 813 (Sept.), 1951.

The authors describe two main patterns of the precordial electrocardiogram which differ in the type of transition of the right sided rS complex to the left sided qR complex. The first type is characterized by large equiphasic (RS) complexes in several leads, usually between V_2 and V_4. Vectorial analysis in the horizontal plane gives a wide and circular loop, and the pattern is therefore termed by the authors "curvilinear." In the other type, there is a more abrupt transition with a small notched or polyphasic QRS in a single precordial lead. Here the horizontal vector loop is narrow, with almost parallel centrifugal and centripetal limbs, pointing with its long axis to the left and backwards. This type of precordial electrocardiogram is called rectilinear. A third type, in which a large and diphasic transitional complex is seen in a single chest lead gives a horizontal vector loop projection with two, more or less rectangular, main axes.

While the first type is seen normally, the second "rectilinear" type was found to be invariably associated with left ventricular hypertrophy. In several cases with otherwise completely normal electrocardiogram, this precordial electrocardiogram was the only manifestation of left ventricular hypertrophy suggested on clinical grounds. The third, biaxial type was present in cases with rheumatic heart disease, of hypertension associated with chronic pulmonary disease, and in left bundle branch block. Here, apparently, the dominant left ventricular (rectilinear) contour of the horizontal projection of the vector loop is distorted by additional forces associated with right ventricular hypertrophy and/or abnormal sequence of activation of the two ventricles.

PICK

Rosenbaum, F. F.: The Place of the Electrocardiogram in Cardiac Diagnosis. Ann. Int. Med. **35:** 542 (Sept.), 1951.

In order to be of real value, an electrocardiogram must be recorded properly. Artefacts may result from many causes. Probably the most common is improper preparation of the patient. Inadvertent interchange of lead wires is another error which seems often to go unrecognized. An electrocardiographic interpretation can be no better than the technical quality of the record from which it is made. The electrocardiogram is the most convenient and generally useful method available for the analysis of cardiac arrhythmias, but to arrive at a correct diagnosis, careful measurement and analysis of the records are sometimes required and, at times, simple clinical physiologic experiments employing exercise, carotid sinus stimulation, or the administration of atropine or amyl nitrite may be required to alter the cardiac mechanism and add information which will permit a correct diagnosis. Additional electrocardiographic observations after trial doses of digitalis, quinidine, procaine or other drugs may be required. When paroxysmal rapid heart action occurs, bizarre QRS complexes do not by themselves permit a diagnosis of paroxysmal ventricular tachycardia. Changes of minor degree which are deviations from the mean are encountered in many electrocardiograms, but their significance is still in question. It seems wiser and more honestly courageous to evaluate such deviations by a careful correlation with the entire clinical picture, and to advise the patient to disregard them if there are no other signs of cardiac disease, than to fall into the falsely secure practice of advising such a patient that he has coronary sclerosis or myocardial strain. The electrocardiogram is the most important diagnostic laboratory aid available in cases of myocardial infarction but it must be remembered that serious heart disease may be present and, in fact, grave calamity may be impending, and yet the electrocardiogram will fail to indicate it. The electrocardiographic changes resulting from some myocardial infarcts are long delayed in their appearance. Abnormalities of significance almost always do occur, but a period of two or three weeks and multiple serial observations may be required. Such patients must be treated on the basis of clinical evidence, and the seeming normality of the electrocardiogram should be ignored. In addition, the alterations produced by an infarct may clear rapidly, in some patients within five to seven weeks. Consequently the diagnosis of an earlier myocardial in-

faction cannot always be excluded, because electrocardiograms taken relatively soon after an episode of severe pain are normal. There is no element in the electrocardiogram which is a direct measure of the functional capacity of the heart. The cardiac function may be entirely normal even though the form of the tracing is grossly abnormal. This is well illustrated in the instances of complete bundle branch block which apparently represent some minor congenital anomaly in the specialized conduction tissues. On the other hand, the electrocardiogram may be within the normal range in patients with congestive heart failure or incapacitating angina pectoris.

WENDKOS

Gros, G., Gordon, A., and Miller, R.: Electrocardiographic Patterns of Normal Children from Birth to Five Years of Age. Pediatrics **8:** 349 (Sept.), 1951.

The authors made a study of 130 electrocardiograms of 104 normal infants and young children ranging in age from a few hours to 5 years.

The electrical position was most frequently vertical or semivertical. The P-P interval ranged from 0.10 second to 0.16 second with an average of 0.12 second. The QRS duration was shorter in the younger age groups and gradually increased with age. The M-shaped, or slurred QRS complexes were occasionally seen in normals. During the first 24 hours of life, the T waves were upright or diphasic in V_{4R}, V_1, V_2, and inverted in V_5 and V_6. However, this gradually changed so that on the fourth day the T wave became inverted in V_{4R}, V_1 and V_2 and upright in V_5 and V_6. During the first 12 weeks of life, a definite right ventricular predominance exists. There is a high R wave in aV_R and V_{4R}. As the left ventricle becomes larger this pattern gradually changes with the involution of the R waves and the evolution of the S waves in the right precordial leads. The dominance of the left ventricle from electrocardiographic patterns is usual at 3 years of age but sometimes is normally delayed until 5 years.

MARGOLIES

Reubi, F., and Bornstein, G.: The Electrocardiogram in the Course of Acute Poliomyelitis. Cardiologia **18:** 321, 1951.

Among 52 cases of acute poliomyelitis, electrocardiographic changes were found in 31 instances. The abnormalities consisted of flattening or inversion of T waves in all cases, deviations of S-T in a number of cases and prolongation of the P-R interval or of the QRS duration in single instances. An abnormal electrocardiogram was found in 80 per cent of severe cases, in 36 per cent of mild forms and in 18 per cent of abortive forms of the disease. In one fatal instance, autopsy revealed subacute myocarditis. The authors conclude that transient involvement of the myocardium in acute poliomyelitis is not rare and may be diagnosed with the help of serial electrocardiograms. Since electrocardiographic changes may persist for several weeks after cessation of fever, systematic follow-up tracings are necessary throughout the convalescence and before physiotherapy is started.

PICK

DeFazio, V., Marsico, F., and Kappert, A.: Vector Analysis of the Electrocardiogram in Some Cases of Neuro-Vegetative Imbalance. Acta Med. scandinav. **140:** 193, 1951.

The authors made a study of nine patients who showed evidence of neurovegetative imbalance of the neurocirculatory type, electrocardiograms displaying low or partially inverted T waves, sometimes accompanied by depression of the S-T segment, and normalization of the electrocardiogram after Gynergin or Hydergin. The vectorial analysis consisted of the calculation of the ventricular gradient ($\hat{G}$), and of the QRS and T vectors using the method of Ashman. In all cases, the ventricular gradient was considerably reduced in magnitude in the tracing made at rest. Furthermore, the ventricular gradient was shifted in a counterclockwise direction in four out of nine cases. The QRS vector was normally placed in all cases. The gradient ($\hat{G}$) showed a definite increase in magnitude after administration of a sympathicolytic agent, an increase which was greater than that which would have been attributable to the increase in the heart rate alone. The T vector shifted in a clockwise direction in all cases.

It is concluded that the abnormality in the ventricular gradient observed in these patients appears to be due to an abnormal behavior of the electrical forces in the heart during repolarization as a result of neurohumoral influences. The normalizing influence of the alkaloids of ergot upon the T vector in these patients in the absence of accompanying significant changes in the heart rate, suggests that these drugs have effects other than that of sympathetic blockade.

ROSENBAUM

Laake, H.: Myocarditis in Poliomyelitis. Acta med. scandinav. **140:** 159, 1951.

The author found that the incidence of abnormal electrocardiograms in 265 patients with acute poliomyelitis proved to be 31.7 per cent. Although these observations were made over a period of nine years, there was no increased incidence in any particular year and there was no significant sexual difference. Abnormal records were more common in patients over 10 years of age. Abnormal electrocardiograms occurred in 53.5 per cent of the spinal cases with paresis of more than two extremities, in 40.5 per cent of the bulbospinal and bulbar cases, 25.5 per cent of the spinal cases of milder type and only 3.2 per cent of the nonparalytic cases. The abnormalities observed consisted of prolonged A-V conduction, coronary sinus rhythm, abnormal P waves in leads II and

III, and changes in the RS-T segments and T waves. The electrocardiographic changes appeared early during the acute phase of the disease, were moderate in degree and tended to be transient in nature. Among the group of 21 patients who died, the electrocardiograms were abnormal in 10 instances. Histologic examination of the heart was performed in only three patients but an interstitial myocarditis quite similar to that described by Fiedler in acute interstitial myocarditis was present in all of them.

ROSENBAUM

Kirkegaard, A., and Nørregaard, S.: Electrocardiogram in Severe Acute Barbiturate Poisoning. Acta Med. scandinav. **140:** 119, 1951.

The material studied comprised 54 patients who were admitted to the hospital in a state of unconsciousness from barbiturate poisoning. Patients with cardiovascular disease or persons taking digitalis were excluded. The electrocardiograms were considered to be definitely abnormal in 33 patients. The unconsciousness lasted 30 hours to five days in this group and nine of them died. The electrocardiograms were abnormal during the first 24 hours in more than one-third of the patients but in the others the abnormalities did not appear until the second, third or fourth day. The changes which appeared consisted of flattening or inversion of the T waves, depression of the RS-T segments, and in some patients, increase in the height of the P waves in lead II. The electrocardiographic changes were attributed to an oxygen deficiency of the myocardium resulting from secondary circulatory shock, the type of edematous swelling of the capillary walls described by Ruhl or the accumulation of secretion in the upper air passages. The possibility of a direct effect of the barbiturate upon the myocardium also exists. The electrocardiographic changes cleared in all patients who survived the poisoning.

ROSENBAUM

Sebastiani, A.: Duration of Electrical Systole during Rest and after Exercise in Normal and Cardiac Subjects. Cuore e circolaz. **35:** 229, 1951.

The author made a comparative study of the variations of the Q-T interval after exercise in 77 subjects which included normal persons and patients with heart conditions. The Q-T interval was calculated according to Bazett's formula. It was observed that exercise is followed by a shortening of Q-Tc in normal subjects and by lengthening of this interval in subjects with heart conditions. According to the author, this reveals the impairment of the heart muscle, because the prolongation is proportional to the severity of myocardial involvement, as shown by the electrocardiogram.

The author suggests that this method be used to evaluate the "reserve power" of the heart.

LUISADA

Coelho, E., Fonseca, J. M., Nunes, A., Padua, F., and Serras Pereira, J.: Intracavity Potentials of the Human Left Ventricle in Various Cardiopathies. Arch. mal. coeur. **44:** 961 (Nov.), 1951.

The authors performed retrograde catheterization of the aorta and the left ventricle and recorded left cavity potentials in 20 cases which included normals, cases with left ventricular hypertrophy, with left or right bundle branch block, aortic insufficiency, mitral stenosis, myocardial infarction and one case of W-P-W syndrome. A convential cardiac catheter was inserted into the radial artery at the lower third of the forearm, and passed without difficulty up to the aortic valves, and in most instances into the cavity of the left ventricle and left auricle. In some cases, the catheter entered the descending instead of the ascending aorta and electrocardiograms were recorded at different aortic levels. The authors state that "no serious accidents or complications" were encountered during the procedure.

With position of the catheter tip in the ascending or descending aorta, epicardial ventricular potentials were obtained, similar to those seen in esophageal leads. Left auricular potentials were recorded in those positions, when the left auricular was enlarged (mitral stenosis), and were similar to simultaneous tracings recorded in the right auricular cavity. Tracings recorded in the left ventricular cavity had various patterns. A QS with an inverted T wave was obtained in normals and right bundle branch block; an RS in left bundle branch block; a qRS or RS with upright T waves was seen in cases with left ventricular hypertrophy and was interpreted by the authors as manifestation of incomplete left bundle branch block. In one instance of right bundle branch block, a transeptal potential was recorded with the help of two catheters placed in the right and left cavity, and indicated activation of the septum from left to right. In the instance of W-P-W, likewise examined by biventricular cathetrization, a shortened P-R interval and a delta wave was found only in tracings from the left ventricular cavity, while the distance P-S was the same and normal in tracings from both cavities. This observation suggests, that in this instance of W-P-W syndrome, pre-excitation of the left ventricle started at the left side of the intraventricular septum.

PICK

Chiaverini, R.: An Electrocardiographic Study of Right Ventricular Strain. Arq. brasil. cardiol. **4:** 249 (Sept.), 1951.

In a series of anesthetized dogs, the authors exposed the heart and submitted the pulmonary artery to acute compression with the object of producing acute right ventricular strain. In addition to this experimental procedure, right ventricular hypertrophy was obtained in six dogs by cellophane involvement of the main pulmonary artery, causing progressive stenosis of this vessel. Similar methods

were applied to the aorta for the purpose of obtaining comparative data on right and left ventricular strain.

The electrocardiographic changes in direct epicardial leads following acute occlusion of the pulmonary artery, varied according to the position of the exploring electrode. Thus, the R/S ratio increased over the trabecular zone of the right ventricle, and decreased over the pulmonary conus and left ventricle. The QRS changes were mainly attributed to a transient incomplete right bundle branch block. Both S-T segment and primary T wave changes were recorded over the right ventricle and were interpreted as due to acute coronary insufficiency. A pulmocoronary vagal reflex could not be demonstrated since both hemodynamic and electrocardiographic changes persisted after full atropinization.

Cellophane involvement of the pulmonary artery determined peri-arterial fibrosis and subsequent pulmonary stenosis which led to variable degrees of right ventricular hypertrophy. Under these circumstances, there was a left axis shift and a decrease of its magnitude. An increased R wave was observed in right precordial leads, although no appreciable widening of the QRS interval could be demonstrated. Direct leads over the epicardial surface of the right ventricle showed increased R waves over the trabecular zone. The possible applications of this study to human electrocardiographic interpretation are discussed.

SCHLESINGER

HYPERTENSION

Roseman, M. D., and Wasserman, E.: The Incidence of Hypertension in Mitral Stenosis. New England J. Med. **245:** 450–53 (Sept. 20), 1951.

In order to test the general belief that hypertension is more common in patients with mitral stenosis the authors made a study of 517 patients with mitral stenosis and 2000 consecutive hospitalized patients of comparable age and sex distribution. The incidence of hypertension, as indicated by systolic pressure levels of 150 or over and diastolic pressures of 90 or over, was 19.9 per cent in the patients with mitral stenosis and 29.1 per cent in the control group. Above the age of 45 years hypertension was present in 31.9 per cent of the mitral stenosis group and 43.4 per cent of the control patients. Hypertension was slightly more common in female patients of all groups studied. The authors conclude from this study that hypertension is no more common in patients with mitral stenosis, whatever the age level or sex, than it is in the general hospital population.

ROSENBAUM

Currens, J. H., Reid, E. A. S., MacLachlan, E. A., and Simeone, F. A.: Metabolic Effects of the Rice Diet in the Treatment of Hypertension. New England J. Med. **245:** 354 (Sept. 6), 1951.

The authors observed the metabolic effects of the rice diet in seven hypertensive patients. A negative nitrogen balance occurred early after the institution of the diet but this decreased greatly after two to three months. A decrease in the basal metabolic rate occurred early, together with a delayed drop in the serum cholesterol. Changes observed in the renal hemodynamics included a general decrease in glomerular filtration, effective renal plasma flow and total tubular excretory mass. The authors considered these changes as possibly only a reflection of the low protein content of the diet and not necessarily an adverse effect. Plasma volume tended to remain the same or to decrease. The blood pressure was thought to be significantly reduced in two patients and there was some downward trend in the remaining five cases.

ROSENBAUM

Werko, L., Wade, Frisk, A. R., and Eliasch, H.: Effect of Hexamethonium Bromide in Arterial Hypertension. Lancet **261:** 470 (Sept. 15), 1951.

The clinical and hemodynamic effects of intravenous hexamethonium bromide in hypertensive patients are reported. Hexamethonium bromide caused a greater fall in systemic blood pressure than did either sodium amytal or tetraethylammonium bromide.

The largest intravenous dose of hexamethonium bromide that can be given safely is regarded as 0.2 mg. per kilogram of bodyweight. Catheter studies in three cases showed a fall in pressure in the pulmonary capillaries and in the pulmonary artery, a decrease in the cardiopulmonary blood volume, and (in two of the three cases) a fall in cardiac output. These changes may be due to pooling of blood in the systemic circuit.

BERNSTEIN

Benchimol, A. B., and Dias Carneiro, R.: The Effect of Pyrogen Treatment in the Severe Forms of Arterial Hypertension. Arq. brasil. cardiol. **4:** 319 (Sept.), 1951.

The authors present a study on the therapeutic possibilities of pyrogenic substances in severe forms of arterial hypertension. Seven patients were treated by this method, of which two belonged to group IV, and five to group III of the Wagener-Keith classification. Treatment was usually of six weeks' duration and was not prolonged further in view of the refusal of most patients to continue this form of medication.

The immediate results were satisfactory in all cases, not only regarding symptomatic relief and a fall in blood pressure, but also as to eyeground and to electrocardiographic changes. Improvement, however, was of exceedingly short duration and did not compensate for the patients' extreme discomfort throughout the therapeutic procedure.

SCHLESINGER

Arst, D. B., Lahey, W. J., and Kunkel, P.: Pheochromocytoma. Yale J. Biol. & Med. **24:** 26 (Sept.), 1951.

The authors present two cases of pheochromocytoma in young adults. In one case, the hypertension was not paroxysmal, in the other, it was sustained but was sharply increased by histamine. The first patient died after an incomplete exploratory operation and the second patient was successfully operated on. The role of various pharmacologic agents in the symptomatology, diagnosis and management are discussed. It is stressed that most of the drug tests can give both false-negative and false-positive results. Since serious reactions can occur in patients with pheochromocytoma receiving histamine and in patients with essential hypertension receiving benzodioxane, the suggestion is made that the latter drug be used when the diagnosis of pheochromocytoma seems probable and that histamine be used as a screening procedure in cases of sustained hypertension when there is no evidence of pheochromocytoma. It is also felt that Arterenol is more useful than epinephrine in preventing postoperative peripheral vascular collapse after removal of the tumor in a case with marked preoperative response to Dibenamine.

ENSELBERG

Emlet, J. R., Grimson, K. S., Bell, D. M., and Orgain, E. S.: Use of Piperoxan and Regitine[R] as Routine Tests in Patients with Hypertension. J.A.M.A. **146:** 1383 (Aug. 11), 1951.

The authors discuss tests made in a routine manner on 62 patients who had persistent hypertensive vascular disease without uremia or, apparently, pheochromocytoma, four hypertensive patients with pheochromocytoma, and eleven patients with hypertensive vascular disease and uremia and no observed pheochromocytoma. A standard intravenous dose (15 mg.) of Piperoxan was used. A standard intramuscular dose (5 mg.) of Regitine was used on another occasion in each patient. The authors feel that Regitine produces less fluctuation of blood pressure and fewer side effects than Piperoxan. False positive reactions may occur with the use of either drug in patients with uremia. The authors feel that a single intramuscular injection of Regitine can be used for routine study of hypertensive patients. Piperoxan may be used as a confirmatory test.

KITCHELL

Lovejoy, F. W., Yu, P. N. G., Bruce, R. A., Nye, R. E., Welch, G., Brody, B. B., and Muxworthy, J.: The Effects of Intravenous Protoveratrine on Hemodynamics and Exercise Tolerance in Patients with Hypertension. Am. J. M. Sc. **222:** 129 (Aug.), 1951.

Protoveratrine is a single crystalline alkaloid derived from veratrum album suitable for intravenous or oral administration. A thorough study of the effect of this compound upon hypertensive subjects was conducted by determining exercise tolerance and physical fitness indices before and after intravenous injection of the drug. Two groups of patients were examined: The first received an average of 0.12 mg. of the drug in the recumbent position; the second received an average of 0.19 mg. in the sitting position. Only four of the 10 patients in group I had a significant fall in blood pressure although a relative bradycardia occurred in the majority. All those in group II manifested a hypotensive effect as well as some improvement in exercise values as determined by the physical fitness index. The physiologic response to exercise, with increases in blood pressure and pulse rate, was not prevented by the drug. Two of the patients manifested electrocardiographic evidence of coronary insufficiency during the test, presumably because of reduced coronary blood flow resulting from the lowered blood pressure.

SHUMAN

PATHOLOGY PHYSIOLOGY

King, B. D., Harris, L. C., Jr., Griefenstein, F. E., Elder, J. D., Jr., and Dripps, R. D.: Reflex Circulatory Responses to Direct Laryngoscopy and Tracheal Intubation Performed during General Anesthesia. Anesthesiology **12:** 556 (Sept.), 1951.

Direct continuous arterial blood pressure and pulse rate were recorded from a brachial artery by means of a Lilly capacitance type electromanometer and direct writing oscillograph on 46 subjects who were intubated during general anesthesia. In 23 of these patients simultaneous electrocardiograms were obtained before and during intubation. During light general anesthesia direct laryngoscopy or tracheal intubation caused a rise in blood pressure and an increased heart rate. These changes were induced by pressure of the instrument on the base of the tongue or by raising the epiglottis, and were more marked on direct tracheal intubation. These phenomena were diminished and abolished by deeper planes of anesthesia and appeared to be independent of the anesthetic agent used and were not changed by the omission of curariform drugs. The degree of circulatory response was variable and unpredictable. During laryngoscopy cardiac arrhythmias were not induced, but were observed with tracheal intubation in lightly anesthetized subjects. Similar studies, performed on dogs, revealed that with light anesthesia these procedures produced bradycardia and a lowering of the blood pressure indicating that the balance between sympathetic and vagal tone in the dog is different from that in man.

SAGALL

Gaderman, E.: Regulation of the Circulation in Dystrophia Musculorum Progressiva (Erb). Ztschr. Kreislaufforsch. **40:** 538 (Sept.), 1951.

In 11 patients with progressive muscular dystrophy the dynamics of the circulation were studied

by the method of Broemse and Ranke. In seven instances, the tests were repeated in standing position and after exercise. In addition, the intramuscular pressure in the biceps and gastrocnemius muscle was determined in all patients.

While a considerable variability of the circulatory data was found at rest, a uniformly normal orthostatic adaptation occurred in all instances. Thus, an elevation of blood pressure followed a change to upright position and the usual slight decline of stroke volume and output per minute was less evident than that seen in normal persons. These regulatory changes of the circulation occurred despite the fact that a lowered intramuscular pressure was found in all instances.

The results of these experiments contradict some of the present concepts concerning the role of contraction and tone of skeletal muscle in the mechanism of venous return to the heart. Thus, in the normal adaptation of the circulation to changes of position, the mechanical effects of variations of intramuscular pressure appear far less important than central neurohumoral factors.

PICK

Bean, J. W., Mayo, W. P., O'Donnell, F., and Gray, G. W.: Vascular Response in Dog Lung Induced by Alterations in Pulmonary Arterial CO_2 Tension and By Acetylcholine. Am. J. Physiol. **166:** 723 (Sept.), 1951.

The authors studied the pulmonary effects of high CO_2 in isolated dog lungs at constant temperature and perfusion pressure. When high CO_2 existed for short periods in the pulmonary artery blood, there was a decrease of blood flow through both ventilated and nonventilated lung. This effect can not be entirely attributed to constriction in the pulmonary blood vessels. The predominant decrease in outflow is due to constriction with simultaneous increase in lung volume. This last indicates vascular dilation and pooling of blood in lungs. The dilation may be either active or a passive reservoir function. Acetylcholine gives results similar to high CO_2. It is suggested that CO_2 in the lung influences vessels directly but may influence nervous control in the intact animal by virtue of its local anticholinesterase action.

OPPENHEIMER

Cockett, F. B., and Vass, C. C. N.: A Comparison of the Role of the Bronchial Arteries in Bronchiectasis and in Experimental Ligation of the Pulmonary Artery. Thorax **6:** 268 (Sept.), 1951.

The authors studied the changes occurring in the bronchial arterial system after experimental ligation of the pulmonary artery in dogs and in a human case of bronchiectasis, using Neoprene bronchovascular casts. One year after tying the pulmonary artery, the bronchial arteries were found to be hypertrophied, dilated and extremely tortuous. The pulmonary artery was decreased in size but was patent distal to the ligature. There were visible communications between branches of the bronchial and pulmonary arteries.

In the case of a left lung removed from a patient because of total bronchiectasis, similar types of large communications were found between the two sets of vessels. There were likewise a great hypertrophy of the bronchial arterial system and a vast network of tortuous vessels derived from this source. However, the pulmonary arteries were shrunken in size.

It was the authors' impression that the communicating channels were dilatations of previously existing vessels and that in the dog they enlarged in response to complete occlusion of the pulmonary artery. However, this theory could not be applied to explain the changes in bronchiectasis, since the pulmonary arteries are considered to be patent in this condition. It was therefore proposed that in severe bronchiectasis these vessels become thrombosed and are then recanalized via the bronchopulmonary anastomoses from the enlarged bronchial arteries. Thrombosis of the pulmonary arteries could then be considered as an adequate stimulus to the development of the bronchial collaterals, in the same way as experimental ligation of the main artery is.

ABRAMSON

Allison, P.: The Measurement of Blood Pressure in Oesophageal Varices. Thorax **6:** 325 (Sept.), 1951.

The author describes a method of obtaining venous pressures in esophageal varices due to portal cirrhosis. An adult medium-sized Negus esophagoscope is used, this being modified by welding into the posterior wall a small peep sight, 2 mm. in diameter, which projects into the lumen of the apparatus on a small pedicle. The peep sight is used to support and steady the needle for puncturing the vein. The needle is bent at an angle of 14 degrees 20 mm. from its tip and it contains a lateral hole located on the opposite side to the bevel.

The pressure readings are obtained in the following manner: The esophagoscope is passed after the patient has received an intravenous anesthetic and the throat is anesthetized locally. A suitable varix is selected on the posterior wall by inspection through the esophagoscope, and then the needle, connected to a Hansen manometer, is passed through the instrument and the vein is pierced. After blood has been drawn back into a syringe attached to a side tube, a pressure is taken. When the needle is withdrawn the esophagoscope is passed over the puncture to compress it for a short time. A little oozing may take place from the site of puncture.

ABRAMSON

Schmidt, A., and Reubi, F.: Cardiac Output, as Obtained by Wezler-Boeger's and Fick's Methods. Cardiologia **19:** 42, 1951.

Comparative determinations of cardiac output were performed in nine cases using both the pulse-wave method of Wezler-Boeger and Fick's method through right heart catheterization

In Wezler-Boeger method the stroke volume is considered directly proportional to the pulse pressure and inversely proportional to the elasticity of the vessels. The values obtained with this method were found much lower than those obtained by the Fick's method, with differences ranging from 11 per cent to 51 per cent (average 41 per cent).

LUISADA

Bierman, H. R.: Pulmonary Circulation Times with Relationship to Acute Hypoxia. Am. J. M. Sc. **222:** 162 (Aug.), 1951.

A method of determining circulation times from lung to ear and from arm to ear has been developed employing the Millikan Oximeter to detect oxyhemoglobin and methylene blue. In measuring the lung-to-ear time (left heart), the patient was prepared by breathing nitrogen until the oxygen saturation dropped to 60 or 70 per cent whereupon a deep inspiration of room air was taken. The circulation time was measured by stop watch from the time of inspiration to the first upward movement of the galvanometer. Repeated determinations at various oxygen saturations produced a curve from which extrapolation of circulation time at 95 per cent oxygen saturation could be calculated. The arm-to-ear circulation time was obtained by injecting 2 cc. of 1 per cent solution of methylene blue through an 18 gage needle into an antecubital vein. The end point was represented by the first downward movement of the galvanometer beam.

In normal subjects, the lung-to-ear time ranged from 4.8 to 7.1 seconds. The rapid circulation time obtained by this procedure may be related to hypoxia induced by nitrogen breathing which causes vasoconstriction in the pulmonary circuit and increases cardiac output. A direct relationship between the lung-to-ear time and arterial hypoxia was demonstrated. The arm-to-ear time in normal subjects varied from 9.6 to 19.9 seconds. No significant untoward effects were noted using methylene blue.

SHUMAN

Lipin, J. L., and Whitehorn, W. V.: Circulatory Adjustments to Reduced Barometric Pressure. J. Aviation **22:** 278 (Aug.), 1951.

The central and peripheral circulatory responses of anesthetized dogs exposed to 35,000 feet simulated altitude while breathing oxygen were studied. The insignificant variations in heart rate, systolic and diastolic pressures and stroke volumes found were in keeping with existing concepts indicating that central circulatory events are unaffected by changes in barometric pressure uncomplicated by hypoxia. Since mean arterial pressures and cardiac minute volumes were not significantly modified, it can be concluded that no important changes in total peripheral resistance took place. However, the results showed definite modifications in peripheral flow during the period of decompression. Skin temperatures showed a significant drop indicating reduced peripheral blood flow during decompression.

The factors responsible for the reduction in peripheral circulation were not determined, but it was suggested that vasomotor reflexes originating in the distended gastrointestinal tract and accessory air sinuses or from accumulations of extravascular gas in body tissues might be responsible for the effects noted.

BERNSTEIN

Levy, M. N., and Berne, R. M.: Effects of Acute Reduction of Cardiac Output upon the Mechanisms of Sodium Excretion in the Dog. Am. J. Physiol. **166:** 262 (Aug.), 1951.

In these experiments the pulmonary artery was partially occluded. This produced a reduction in the cardiac output. Under these conditions clearance of sodium was reduced at both normal and elevated plasma concentrations. Most often the absolute rate of tubular reabsorption of sodium is decreased but the reabsorbed fraction of sodium presented to the tubules is increased. The authors are of the opinion that a decreased glomerular filtration rate best explains the decreased sodium clearance. The reduced glomerular filtration rate is secondary to a lower cardiac output. It is concluded that changes of sodium levels, renal venous pressure, and arterial pressures, in these experiments, may have affected the sodium elimination, but that their role was only minor.

OPPENHEIMER

Robertson, W. Van. B., and Peyser, P.: Changes in Water and Electrolytes of Cardiac Muscle Following Epinephrine. Am. J. Physiol. **166:** 277 (Aug.), 1951.

This paper presents the results of water and electrolyte analyses on the myocardium of cats after intravenous injection of epinephrine. Both epinephrine and Arterenol increased extra cellular fluid volume of heart muscle. Single doses of 500 μg. of epinephrine increased intracellular sodium and decreased intracellular potassium. Smaller amounts were ineffective.

OPPENHEIMER

Bacchus, H.: Decrease of Cardiac Mass Following Excess Dietary Potassium Chloride in the Rat. Am. J. Physiol. **166:** 273 (Aug.), 1951.

Rats were maintained on a regimen which included 2.5 per cent KCl as the only source of liquid. Results of the experiments indicate that dietary excess of KCl in rats produces hypertrophy of the glomerular zone in the adrenal cortex, renal hyper-

trophy, and a decreased cardiac weight. If KCl is withdrawn, these results are reversible.

OPPENHEIMER

Wilhelmj, C. M., Waldmann, E. B., and McGuire, T. F.: Basal Blood Pressure of Normal Dogs Determined by an Auscultatory Method and a Study of the Effect of Fasting. Am. J. Physiol. **166:** 296 (Aug.), 1951.

Fasting blood pressure is very constant in any one dog. The previous nutritional state is not important to the level but does influence the rate of fall of pressure and pulse rate to the stable fasting level. When the nutritional level is high the pressure fall to basal levels requires a long time. If the prefasting nutritional level is low the fall is rapid. Pulse rate behaves in a similar manner in most cases.

OPPENHEIMER

Cranfield, P. F., Eyster, J. A. E., and Gilson, W.: Effects of Reduction of External Sodium Chloride on the Injury Potentials of Cardiac Muscle. Am. J. Physiol. **166:** 269 (Aug.), 1951.

Turtles hearts were injured by a suction electrode. When such hearts are perfused with a solution containing only one third of the control value for sodium both positive and negative values of injury potentials are reduced. Positive phases are reduced more. The authors conclude that the positive phase may be associated with increased permeability of muscle to sodium. Others have described this for nerve and skeletal muscle.

OPPENHEIMER

Fleetwood, M. F.: Determination of Adrenergic Substance in Blood Related to Anxiety. Identification as Nor-Adrenaline. Am. J. Physiol. **166:** 314 (Aug.), 1951.

The present study is an attempt to determine whether the adrenergic substance that is increased in the peripheral blood during anxiety is epinephrine or norepinephrine. This substance resembles norepinephrine because the effects on rat uterus were only 4 to 6 per cent of that on rabbit duodenum and rat colon. Ergotamine does not change the effect. The most sensitive indicator for epinephrine is rat uterus. Therefore the fact that the responses to the unknown substance were so small demonstrates that the substance can not be epinephrine. Absence of ergotoxine effect also supports this. Rat colon and rabbit intestine are very sensitive to the unknown substance. Norepinephrine is the only substance which gives results similar to those obtained in these instruments. The author feels justified in concluding that the substance that is increased in the blood during excitement is similar to norepinephrine.

OPPENHEIMER

PATHOLOGY

Etheridge, C. L., Sando, D. E., and Foltz, E. F.: Dissecting Aortic Aneurysm. Quart. Bull. Northwestern Univ. M. School **25:** 221 (Fall), 1951.

The authors believe that dissecting aortic aneurysm is more common than it is usually considered to be and its autopsy incidence is increasing along with other diseases of old age. Stress acts in summation with a defective media in producing dissection. The stress may be a prolonged organically-based hypertension or a transitory hypertension, as in emotional stress or physical exertion.

Cystic medial degeneration, of varying description, is the most frequently implicated cause of defection in the media. The causes of medial degeneration are probably multiple and include congenital defect, disturbances in metabolism and the process of aging, and disease or altered hemodynamics of the vasa vasorum. Dissection initiates as a hematoma within a defective media and an intimal tear need not occur.

The initial symptoms of pain, syncope, and collapse are suggestive, but not diagnostic. Differentiation from commonly confused diagnoses is usually made by taking into account the manifestations of occlusion of aortic branches. The presence of signs of heart disease should not mitigate against the diagnosis of dissecting aneurysm.

Electrocardiograms may reflect positional change, or myocardial ischemia due to alterations in the hemodynamics of the coronary arteries by the dissection, directly or indirectly, and show changes suggestive of myocardial infarction.

Neurologic manifestations are most frequently transitory, but infarction of the brain, spinal cord, or peripheral nerves may occur.

BERNSTEIN

Bangston, E., Birke, G., and Winstrand, H.: Acute Non-specific Myocarditis in Scarlet Fever and Acute Hemolytic Tonsillitis. Cardiologia **18:** 360, 1951.

The authors studied 3069 nonselected cases of scarlet fever, seen during an epidemic in Stockholm, for the presence of myocarditis. The study was then extended to 798 cases of tonsillitis due to hemolytic streptococcus and to 333 carriers of the latter organism.

The incidence of myocarditis was 3.9 per cent in the first group, 4.4 per cent in the second group and zero in the last. In the first two groups it was about three times higher in adults than in children. In approximately half of the cases with myocarditis the condition started as early as in the first week of the illness and lasted in the majority of cases not more than a few weeks. However, the complicating myocarditis prolonged the time of convalescence compared with cases without cardiac involvement.

The diagnosis of myocarditis was made on the basis of a collective clinical appraisal including

tachycardia, appearance of murmurs and/or gallop rhythm, increase of the sedimentation rate and the antistreptolysin titer and electrocardiographic alterations. In about 60 per cent of the cases, more than one of the clinical signs were present. However, none of them were seen as constantly as alterations of the electrocardiogram. The latter consisted in alterations of ST-T, prolongation of P-Q and Q-T intervals, deformation and widening of QRS and appearance of ectopic rhythms. Alterations of the ventricular complex were found most frequently (10 to 15 per cent).

PICK

Van Buchem, F. S. P., Nieveen, J., and Verhey, J. B.: Isolated Stenosis of the Pulmonary Artery. Cardiologia **19:** 248 (fasc. 4), 1951.

The authors present clinical, radiologic and electrocardiographic observations in eight cases of isolated pulmonary stenosis, proven by cardiac catheterization. The age of the patients varied between 13 and 42 years, and all had a loud systolic murmur, frequently associated with a thrill, in the first to third left intercostal space and transmitted to the back. The second pulmonic sound was frequently, but not invariably, muffled. At x-ray examination, poststenotic dilatation of the pulmonary artery was present in six and absent in two instances. Delay of left ventricular filling at angiocardiography was found only in part of the cases and in one instance the authors succeeded in demonstrating by this method the site and the type of the lesion. In none of the cases was the electrocardiogram diagnostic of right ventricular hypertrophy though pressure elevation in the right ventricular cavity was found in all at cardiac catheterization. The pulmonary artery could be entered in all cases, and in some of them it was possible to differentiate between valvular and infundibular stenosis under consideration of the contour of the pressure curves. In one instance a combination of both types of stenosis was diagnosed.

The authors insist, that the presence of a small, dynamically insignificant intracardiac shunt can never be ruled even by cardiac catheterization. The observations prove that an "isolated" pulmonary stenosis, even if of advanced degree, need not be associated with radiologic and electrocardiographic changes, so that the diagnosis cannot be made without cardiac catheterization.

PICK

Lippert, K. M., Potozky, H., and Furman, I. K.: Clinical Significance Of Pleuropericardial Cyst. Arch. Int. Med. **88:** 378 (Sept.), 1951.

The authors present three surgically proved cases of pleuropericardial cyst, with a description of the clinical methods used in arriving at the diagnosis.

A pleuropericardial or pleurocelomic cyst is a thin-walled structure, typically occupying the right cardiophrenic angle. It is covered by pleura and lined by endothelial-like cells, whereas the wall itself is made up of poorly defined fibrous tissue. The cystic fluid is not unlike that encountered in the pericardium, having a low specific gravity, low protein content, and few, if any, leukocytes. The mode of origin is not specifically understood, but careful comparison of opinions indicates the acceptance of a theory that the cyst results from a developmental irregularity of the lacunas in the primitive mesenchyma. Roentgenologic examination, employing pneumothorax, pneumoperitoneum, bronchography and angiocardiography, is the principal means of diagnosis. However, in selected cases, aspiration may give conclusive evidence. Surgical treatment is indicated when the cyst becomes so large as to cause dyspnea and pain, and when differential diagnosis fails to show conclusively the character of the tumor.

BERNSTEIN

AMERICAN HEART ASSOCIATION, INC.

1775 Broadway, New York 19, N. Y.

Telephone Plaza 7-2045

ASSOCIATION FELLOWSHIPS

Applications for Established Investigators and for Research Fellows must be received not later than September 15, 1952. Information and forms may be obtained from the Medical Director.

RESEARCH GRANTS-IN-AID APPROVED

Seventy-two grants-in-aid to institutions in the total amount of $361,522.10 for research studies have been approved by the Board of Directors upon recommendation of the Research Committee of the Scientific Council. The awards, which are for the fiscal year beginning July 1, 1952, are in addition to the Established Investigators and Research Fellows announced earlier this year.

The awards follow:

Continuing Grants-in-Aid

Cornell University Medical College, New York, $8,085, relationship between increased activity of the adrenal cortex and posterior lobe of the pituitary gland and fluid and electrolyte retention in edema, by *Robert F. Pitts.*

Tulane University of Louisiana School of Medicine, New Orleans, $9,135, cytochemical and histochemical approaches to renal physiology, with particular reference to electrolyte reabsorption in congestive failure, by *Nathaniel B. Kurnick.*

Tulane University of Louisiana School of Medicine, New Orleans, $3,675, hemodynamic and iron storing function of ferritin, with particular reference to the kidney, by *H. S. Mayerson.*

Duke University School of Medicine, Durham, N. C., $5,250, response of the pulmonary vascular bed to hemodynamic alterations in the systemic circulation, by *James V. Warren.*

Mary Imogene Bassett Hospital, Cooperstown, N. Y., $7,140, correlation of the morphologic and metabolic aspects of cell damage, by *Joseph W. Ferrebee.*

Oklahoma Medical Research Institute, Oklahoma City, $4,200, influence of adrenal cortical hormones on cardiac lesions and enzymes, by *Charles D. Kochakian.*

University of Pennsylvania School of Medicine, Philadelphia, $10,500, biochemical pathways by which cholesterol and fat are synthesized and metabolized in the body. The action of hormones upon the biosynthesis of cholesterol and lipids, by *Samuel Gurin.*

Yale University School of Medicine, New Haven, $3,885, metabolic basis for heart failure and for treatment of same, by *William T. Salter.*

State University of New York, Medical Center, Syracuse, $4,515, nervous control of water and electrolyte excretion by the normal kidney, by *Otto W. Sartorius.*

New England Center Hospital, Boston, $5,250, physiologic investigation of experimental isolated pulmonary insufficiency and pure right-sided heart failure, by *C. Stuart Welch.*

Harvard Medical School, Boston, $4,200, relationship of the adrenal to hypertension, by *George W. Thorn.*

University of Michigan Medical School, Ann Arbor, $5,880, cardiac metabolism as re-

lated to epinephrine-induced arrhythmias and tachycardia, by *Mark Nickerson.*

University of Minnesota Medical School, Minneapolis, $6,825, investigation of etiologic and pathogenic mechanisms in rheumatic fever as revealed through studies of basic relationships of immunologic, endocrinologic, and biochemical events to pathologic processes related to those responsible for rheumatic disease, by *Robert A. Good.*

Western Reserve University School of Medicine, Cleveland, $3,864, to study *in vivo* the microscopic changes in the circulating blood and the reactions of small blood vessels in patients with heart disease and thrombo-embolism receiving anticoagulant therapy, by *Edward H. Bloch.*

Massachusetts General Hospital, Boston, $4,725, factors that regulate extracellular fluid volume in the normal and edematous subject, by *Alexander Leaf.*

Marine Biological Laboratory, Woods Hole, Massachusetts, $10,000, molecular mechanism of muscular contraction, by *Albert Szent-Györgyi.*

Council on Rheumatic Fever and Congenital Heart Disease, $3,500, cooperative research study of the relative effectiveness of ACTH and Cortisone in the treatment of rheumatic fever and prevention of rheumatic heart disease.

New Grants-in-Aid

Medical College of Georgia, Augusta, $4,462.50, comparative effects of the adrenolytic agents on the cardiovascular system of the dog when administered in the presence of humoral or neurogenic hypertension, by *Raymond P. Ahlquist.*

Bowman Gray School of Medicine, Winston-Salem, N. C., $3,150, study of immunophysiology, by *Jerry K. Aikawa.*

Hahnemann Medical College and Hospital, Philadelphia, $5,250, investigation of the cardiovascular and respiratory dynamics in patients with valvular deformities before and after surgery, by *Charles P. Bailey.*

La Rabida Jackson Park Sanitarium, Chicago, $5,302.50, nature and mode of action of the substance in testicular extract causing increased vascular permeability, by *Earl P. Benditt.*

Temple University School of Medicine, Philadelphia, $2,625, nature of endocarditis and glomerulonephritis in animals with arteriovenous fistulas, as well as obtaining more information on factors influencing susceptibility to these diseases, by *J. Richard Bobb.*

Mary Imogene Bassett Hospital, Cooperstown, N. Y., $5,250, lung volume restriction as a respiratory stimulus in normal subjects and patients with cardiorespiratory disease, by *James Bordley III.*

Columbia University College of Physicians and Surgeons, New York, $3,675, renal and hepatic vascular reactivity in glomerulonephritis, essential hypertension and cirrhosis, by *Stanley E. Bradley.*

Johns Hopkins University School of Medicine, Baltimore, $3,675, autonomic effects of cerebral cortex on experimental renal hypertension, by *Kenneth M. Browne.*

Massachusetts Institute of Technology, Boston, $6,300, chemical investigation of the heart, active principle of Crataegus (Hawthorne), by *George H. Buchi.*

Cornell University Medical College, New York, $4,971.35, effects of drugs and poisons on the action potentials and automaticity of heart muscle, by *McKeen Cattell.*

Fels Research Institute, Antioch College, Yellow Springs, Ohio, $7,350, application of the Fels Oxygenator in prolonged by-pass of heart and lungs, by *Leland C. Clark and Frank Gollan.*

University of Pennsylvania, Graduate School of Medicine, Philadelphia, $6,300, measurement of the work of breathing and pulmonary function in patients with dyspnea, by *Julius H. Comroe.*

University of Pittsburgh, School of Medicine, Pittsburgh, $6,195, cardiovascular effects of cation and anion depletion by vivo-dialysis, by *F. S. Danowski.*

Wayne University, Detroit, $6,184.50, isolation, chemical proof of structure and pharmacologic examination of the heart poison from Pilocereus Sargentianus Orcutt, by *Carl Djerassi.*

Faculty of Medicine, McGill University,

Montreal, $5,013.75, studies tracing fate of labelled cellular elements in atherosclerotic lesions in rabbits fed cholesterol, by *G. Lyman Duff.*

University of California, San Francisco, $3,675, water distribution and water kinetics in patients with edema, by *Isidore S. Edelman.*

University of Pennsylvania, School of Medicine, Philadelphia, $4,200, studies on the supra-optico-hypophyseal system in the normal dog pertaining to volume regulation; and effort to provide at least a partial explanation of certain phenomena observed in markedly edematous patients with heart disease, by *J. Russell Elkinton and Russell D. Squires.*

State University of New York, Syracuse, $4,410, study of some substrates and enzyme inhibitors on cardiac muscle, by *Alfred Farah.*

American University of Beirut, Beirut, Lebanon, $4,725, effect of Krebs cycle inhibitors on the performance and metabolism of the isolated mammalian heart and the effect of cortical hormones on the salt and water excretion in a heart-lung-kidney preparation, by *George Fawaz.*

University of Maryland Medical School, Baltimore, $5,166, factors causing obesity and the influence of obesity in the development of arteriosclerosis and other cardiovascular diseases, by *Frank H. J. Figge.*

University of Cincinnati, College of Medicine, Cincinnati, $5,250, nature of the vascular response to sodium restriction, by *Eugene B. Ferris and Albert A. Brust.*

Mount Sinai Hospital, New York, $3,675, volume of the respiratory dead space and the composition of alveolar gas in subjects with cardiopulmonary disease, and the continuation of studies on congestive heart failure in dogs, by *Alfred P. Fishman.*

Mount Zion Hospital, San Francisco, $6,300, concerning the metabolism of cholesterol, by *Meyer Friedman.*

Georgetown University, School of Medicine, Washington, D. C., $5,250, hemodynamic studies in dogs using a variable heart pump permitting independent control of rate, output and ejection velocity, by *Edward D. Freis.*

Washington University, School of Medicine, St. Louis, $5,250, metabolic factors in experimental heart failure, by *Robert F. Furchgott.*

Johns Hopkins University School of Medicine, Baltimore, $5,250, analysis of the role of the personal factor and of certain drugs in experimental tachycardia, by *W. Horsley Gantt.*

Institute for Medical Research, Los Angeles, $3,780, capillary circulation in experimental renal hypertension in dogs, by *Harry Goldblatt.*

Yale University School of Medicine, New Haven, $5,775, hemodynamic factors affecting electrolyte metabolism and the renal excretion of electrolytes, by *Allen V. N. Goodyer.*

Bowman Gray School of Medicine, Winston-Salem, N. C., $4,830, nature of and the factors leading to the production of the vasoconstriction and the vasodilation which develops in perfused organs, by *Harold D. Green.*

University of California, Berkeley, $5,250, tracer studies of the intermediate metabolism of amino acids and related compounds of significance for hypertension and arteriosclerosis, by *David M. Greenberg.*

University of California, Berkeley, $525, in aid of the investigation of steroid metabolism and possible relations to cardiovascular disease, by *David M. Greenberg.*

University of Utah, School of Medicine, Salt Lake City, $6,300, pharmacology, physiology, and biochemistry of the heart, by *Stewart C. Harvey.*

Presbyterian Hospital, Chicago, $4,200, identification of the conduction system of the heart, by *George M. Hass.*

University of Tennessee, School of Medicine, Memphis, $5,250, role of the heart, blood vessels, liver and altered body fluids in the hypertension arising in dogs living a month or longer without kidneys, by *C. Riley Houck.*

Columbia University, College of Physicians and Surgeons, New York, $4,200, cardiovascular problems related to surgery, by *George H. Humphreys, II.*

University of Utah, School of Medicine, Salt Lake City, $5,250, adrenal hormones in the blood of patients with rheumatic fever and related conditions, by *Vincent C. Kelley.*

University of Tennessee, School of Medicine, Memphis, $2,992.50, role of ventricular

filling in the production of the heart sounds with special attention to the etiology of the first and third sound, by *Robert C. Little.*

Washington University Medical School, St. Louis, $2,940, isolation of specific heart proteins which bind cardiac drugs, by *Oliver H. Lowry.*

State University of New York, School of Medicine, Syracuse, $525, effects of ethyl alcohol and acetaldehyde on the metabolism of the myocardium and other tissues, by *Samuel Mallov.*

Peter Bent Brigham Hospital, Boston, $5,250, investigation into the relation of renal failure to certain disorders of the cardiovascular system, by *John P. Merrill.*

Dartmouth Medical School, Hanover, N. H., $3,150, further development and application of electrical impedance methods to the measurement of various cardiac and circulatory problems, by *Jan Nyboer.*

University of Pittsburgh, School of Public Health, Pittsburgh, $8,925, effect of congestive heart failure due to valvular disease upon myocardial metabolism in dogs, by *Robert E. Olson.*

New York University-Bellevue Medical Center, New York, $5,670, experimental studies on methods for the interruption of the cardiac and pulmonary circulations by refrigeration and with a new type of oxygenator, by *John J. Osborn.*

Mount Zion Hospital, San Francisco, $4,200, role of potassium in maintenance of blood pressure and peripheral vascular reactivity in normotensive and hypertensive states, by *Ray H. Rosenman.*

University of Washington, School of Medicine, Seattle, $5,250, factors influencing diastolic filling and systolic emptying of the ventricular chambers, by *Robert F. Rushmer.*

University of Wisconsin, School of Medicine, Madison, $4,200, mechanism of pyruvate and a-ketoglutarate oxidation in heart muscle, by *D. Rao Sanadi.*

Ohio State University, School of Medicine, Columbus, $5,250, changes in the ionic composition of the intracellular fluid in experimental and clinical hypertension, by *Leo A. Sapirstein.*

Bowman Gray School of Medicine, Winston-Salem, N. C., $2,625, experimental and clinical studies of acute and chronic disorders of the pericardium, by *C. Glenn Sawyer.*

Harvard Medical School, Boston, $4,200, studies on coronary heart disease, by *Monroe J. Schlesinger.*

Mount Sinai Hospital, New York, $3,150, evaluation of the role of the kidney in the pathogenesis of heart failure, by *Jonas H. Sirota.*

Michael Reese Hospital, Chicago, $4,200, factors regulating renal function and electrolyte metabolism in experimental venous congestion with edema, by *Jeremiah Stamler.*

New England Center Hospital, Boston, $5,250, relation of the endocrine system to the blood coagulation mechanism and to the pathogenesis of thrombo-embolism; possibilities of employment of fibrinolysin and fibrinolytic substances in the treatment of thrombo-embolism, by *Mario Stefanini.*

University of North Carolina, School of Medicine, Chapel Hill, $9,450, evaluation of the Macacus rhesus monkey as an experimental animal for the production of atherosclerosis including studies on cholesterol metabolism using C^{14} labeled acetate, by *C. Bruce Taylor.*

Harvard Medical School, Boston, $4,200, biochemical comparison of hypertensive and normal arteries, with particular attention to the electrolyte and intermediary metabolism, by *Louis Tobian, Jr.*

Albany Medical College, Albany, N. Y., $5,250, a physiologic quantitation of the progressive effects following production of mitral stenosis and/or insufficiency by means of implanted plastic prostheses, by *Harold C. Wiggers.*

GIFT FROM AMERICAN TRUST CO.

The American Trust Company of New York City has contributed $2,500 to send research investigators of the Association to the Fourth Interamerican Cardiological Congress being held in Buenos Aires, September 1–6, 1952. Lewis Dexter, Boston, and G. B. Perera, New York, have been approved by the Board to attend the Congress.

REGISTRY OF CARDIOVASCULAR PATHOLOGY

Dr. Thomas M. Scotti, former Associate Professor of Pathology at the Medical College of Virginia, has been appointed Registrar of the Registry of Cardiovascular Pathology in Washington. The Registry, which is sponsored by the American Heart Association, is a division of the American Registry of Pathology, a department within the Armed Forces Institute of Pathology, under the auspices of the National Research Council.

Dr. Scotti succeeds Dr. Henry W. Edmonds, who has become Acting Curator of the Medical Museum of the Institute. Dr. Edmonds continues his interest in the Registry as Associate Registrar.

The Registry welcomes gifts of interesting or instructive cases in the cardiovascular field. It maintains a permanent file of contributed gross specimens, tissue blocks and microscopic slides, correlated with clinical histories, electrocardiograms and x-ray films.

By the end of 1951, the Registry had collected a total of 695 specimens, including 339 on malformations of the heart, 172 cases of endocarditis, 145 in the collagen disease series, and 20 specimens in the neoplasm series. In addition, there are nine miscellaneous cases and 10 with diagnoses in more than one series. Nearly half of these specimens have been donated by individual contributors, with the balance being supplied by the Armed Forces and Veterans Administration.

Forms to accompany cases sent to the Registry may be obtained from the Director, Armed Forces Institute of Pathology, Washington 25, D. C.

The Registry concentrates efforts, for the time being, on cases falling within the following categories:

1. Congenital anomalies of the heart and larger blood vessels
2. Subacute bacterial endocarditis
3. The so-called "diseases of the collagen system" including polyarteritis nodosa, temporal arteritis, disseminated lupus erythematosus, Libman-Sacks endocarditis, scleroderma, and amyloidosis of the heart.
4. Primary tumors of the heart, pericardium, blood vessels and lymphatics, including rhabdomyomatosis and glycogen-storage disease.

In addition, cases will be welcomed from other types of diseases of the heart and larger blood vessels, in which consultation is desired, or in which there is especial interest because of rarity or noteworthy clinicopathologic correlation.

The Registry of Cardiovascular Pathology provides consultation service at a national level in the field of cardiovascular pathology. It is intended that cases submitted for consultation be first examined by a local pathologist, who will refer to the Registry the relevant specimens. Full cooperation of the attending clinician is sought in supplying the pertinent clinical data.

The Registry contemplates preparation of sets of teaching material, available on loan to students and physicians. As the material in the Registry increases, it will be made available to interested investigators upon application to the Director of the Armed Forces Institute of Pathology.

FELLOWSHIP IN PEDIATRIC CARDIOLOGY AVAILABLE

The Children's Division of Cook County Hospital in Chicago has an opening for a Fellow in Pediatric Cardiology. Training in angiocardiography and catheterization will be available, if desired. For further details, communicate with Dr. Benjamin M. Gasul, 700 South Wood Street, Cook County Children's Hospital, Chicago, Illinois.